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DERMOID CYSTS*

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BOSTON

ALTHOUGH dermoid cysts are not common and are seldom malignant, they are of interest from several points of view. When they occur near the body surface they are of concern to the patient because of their conspicuousness or because of his fear of cancer. They are of interest to the surgeon[1-3] from the standpoint of differential diagnosis and complete surgical removal of the lesion. Dermoid cysts of the ovary in particular are subject to a number of complications that may make surgical intervention urgent.

This paper deals with 146 dermoids of the entire body seen at the Lahey Clinic from 1930 to 1952. The distribution of these cases is shown in Table 1. There were no dermoids of the back, testis or extremities. Ovarian dermoids made up 68.5 per cent of the total number; 24.6 per cent involved the head and neck, and the remaining 6.9 per cent were located in the chest and pelvis. Pilonidal cysts and sinuses were not included in this study.

EMBRYOLOGY AND PATHOLOGY

New and Erich[4] have divided dermoids into three types, depending on their pathogenesis and their gross and microscopical appearance.

Congenital Dermoid Cysts

Congenital dermoid cysts are most commonly found in either the ovary or the testis. They are complex in nature, and many studies have shown that in most cases all three germinal layers can be distinguished, although the ectodermal one is usually the most prominent. There are two dominant embryologic theories regarding their development. In one, the blastomere theory, it is thought that some cells become separated from the developing blastomere and lie dormant; later, owing to some chemical or hormonal stimulus, these dormant cells grow and evolve into a dermoid or teratoma. The second theory[5] is that the origin of these tumors seems best explained by the hypothesis of the abnormal development of unfertilized ova as evidenced by the fact that the majority of ovarian dermoids appear during the period of reproductive activity. They are usually thick walled and contain elements derived from any one of the three germinal layers, such as hair, skin, teeth, glandular tissue and bone.[6]

Ovarian dermoid tumors are usually round to ovoid and vary in diameter from 8 mm. to 30 cm.[7] In our series the largest was 23 by 15 cm., and the smallest 0.6 by 0.6 cm., with an average of 6.1 by 7.5 cm. The size of the various tumors found could not be related to the patient's age. The frequency of bilateral dermoids has been reported as varying from 10[6,8] to 25[9] per cent. In the present series bilateral dermoids were found in 7 per cent. No predilection for either ovary has been noted. In this series 47 per cent were on the right side, and 45 per cent on the left. The capsule of the tumor is smooth and usually white or pale yellow. At body temperature the contents are fluid, and the tumor feels cystic. After extirpation, however, the contents congeal, and the tumor is doughy to palpation. Calcium or bone may at times be palpated in the cyst wall. The tumor may or may not be loculated, and contains a sebaceous material in which wisps or tufts of hair are usually found. In this series 29 per cent were loculated, and 71 per cent were simple cysts. Other organoid structures sometimes seen are teeth, bone, cartilage, special sense organs, central nervous system, portions of the intestinal canal, elements of the respiratory tract, muscle, connective tissue, prostate, thyroid gland and sebaceous and sweat glands. The contents of the ovarian dermoids in this series are listed in Table 2 in order of frequency. These tumors are considered benign, although secondary malignant degeneration has been reported in approximately 1 per cent[10] of all dermoid cysts. This malignant change is usually in the form of sarcoma or carcinoma.[9]

Congenital Inclusion Dermoids

This type develops along the lines of embryonic fusion, such as the midventral and mid-dorsal lines

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and the branchial clefts. They develop from inclusions of displaced dermal cells in these areas. The walls of the cysts are lined by stratified squamous epithelium, which contains hair follicles and sweat and sebaceous[11] glands, as opposed to epidermoid inclusion cysts, which are lined by squamous epithelium without those secondary appendages.[12] Luongo[13] offers the following explanation:

> In the early embryo, the frontonasal plate, which forms the nose, consists of a lamina of hyaline cartilage covered externally with skin and internally with mucosa. After the third month of embryonal life, bony tissue extends in between the cartilage and skin. The bony tissue will form the nasal bones. The cartilage becomes absorbed during the process of ossification. During the gradual separation of the skin from the cartilage of the frontonasal plate by the intrusion of the nasal bones, small portions of the skin or epithelium become sequestrated and develop into dermoid cysts.

Dermoids of the scalp, as explained by several authors, occur in a similar manner from the developing cranial bones, which lie between the embryonic skin and dura. As the bones grow toward each other to form the suture lines, groups of dermal cells become cut off from the surface epithelium, resulting in the formation of the dermoid cyst. The cysts are filled with a greasy, grumous material that is often mixed with hair and is nonodorous unless infected. This material is composed of keratinized material, partially cornified cells and granular débris. The cysts vary in size from a few millimeters to several centimeters. The 46 nonovarian dermoid cysts in this report belong in this classification.

TABLE 1. *Distribution of Cases.*

LOCATION	NO. OF CASES	PERCENTAGE
Head & neck	36	24.6
Chest	2	1.4
Presacral	8	5.5
Ovary	100	68.5

Acquired Implantation Dermoids

These occur secondary to trauma in which a portion of skin is driven into the deeper structures and there develops as a cyst lined by squamous epithelium. They are especially common in the hands of laborers and on other exposed parts of the body. These have been classified as epidermoid inclusion cysts and are not taken up in this study.

Clinical Data

The dermoids in this study have been divided into two groups: the first includes 46 dermoids exclusive of ovarian dermoids, and the second ovarian dermoids, of which there were 100. Further analysis of the first group (Table 1) reveals 36 dermoids (24.6 per cent) of the head and neck, 2 (1.4 per cent) of the chest, and 8 (5.5 per cent) of the presacral area. The second group of 100 ovarian dermoids constitutes 68.5 per cent of the total number.

Nonovarian Dermoid Cysts

All lesions in the first group were simple cysts except 2 of the presacral dermoids, which were loculated. Hair was found in 50 per cent. Several cysts showed inflammatory changes, especially those in the presacral region (6 out of 8) and those of the nose (2 out of 3). Other tissues were present in 3 cysts; 1 presacral cyst contained bone, a second presacral cyst contained teeth, and in the third, a dermoid of the nose, nerve tissue was found.

All but 3 of the lesions were completely excised. Of these, 1 was incised and drained, and the cyst wall painted with iodine; another was biopsied and drained, and the third was partially excised, curetted, cauterized and drained. Seventeen per cent of the patients had had previous attempts at excision or had had incision and drainage.

Head and neck. This group of 36 cysts is subdivided into cysts of the scalp, orbit, nose, submental region, neck, tongue and head.

Scalp. There were 3 patients in this group, 2 males, thirty-four and thirty-five years of age, and 1 female, eleven weeks old. The preoperative diagnosis in the child was meningocele. The cysts averaged 2.5 cm. in greatest diameter. They were located as follows: 1 at the right parieto-occipital suture line, 1 at the anterior fontanel and 1 at the bregma. Two contained hair; no other tissue was present. All were excised, and there were no recurrences.

TABLE 2. *Contents of Ovarian Dermoid Tumors.*

CONTENTS	PERCENTAGE
Hair	91
Bone	13
Teeth	12
Calcium	12
Skin	6
Cartilage	5

Orbit. There were 11 patients with orbital cysts, 6 females and 5 males. Their ages ranged from one and a half years to fifty-six years, with an average age of twenty-five and eight-tenths years. Six of the cysts were known to have been present since birth; 3 had been present for four, five and ten years, respectively, and in 2 the duration was not noted. The cysts measured from 0.5 cm. to 5 cm. in greatest diameter. Hair was present in 6, or 55 per cent, and no other tissue was found pathologically. All patients came to the clinic because of the presence of a mass; 2 patients had had previous excisions. The locations of the cysts were as follows: 9 in the supraorbital area, 4 on the right and 5 on the left; 1 on the right eyelid, and 1 on the right inner canthus. In this last case two masses were present; one proved to be a basal-cell carcinoma, and the other a dermoid cyst. The preoperative diagnosis was dermoid cyst in 5 cases, sebaceous cyst in 3, lipoma in 1, lacrimal-gland cyst in 1 and basal-cell carcinoma in 1. All were excised, and there were no known recurrences.

Nose. There were 3 patients in this group, 2 females and 1 male. Their ages ranged from eighteen months to thirty-three years. The mass was known to have been present since birth in all cases. One patient had had two previous, unsuccessful excisions; 2 patients had draining sinuses, and 1 a mass. The cysts varied in size from 0.7 cm. to 2.3 cm. in greatest diameter. Hair was present in 1. One cyst showed nerve tissue on microscopical section. At operation 2 of the cysts had fiber-stalk extensions between the nasal bones into the septum. All 3 cysts were excised; a moderate amount of drainage occurred postoperatively and persisted for a month or two. There was no case of recurrence.

Submental region. Four patients came to the clinic because of a mass in the submental region. The ages ranged from eighteen to forty years; there were 3 males and 1 female. The average size of the cysts was 3 cm. in greatest diameter. All 4 were simple cysts; hair was found in 2, and no other tissue was present. The preoperative diagnosis was thyroglossal cyst in 3 and Hodgkin's disease in 1 — a patient with associated lymphadenopathy. Three were excised, and a fourth was incised, drained and cauterized with iodine. There were no recurrences.

Neck. In this group there were 11 cysts measuring from 2 to 10 cm. in greatest diameter. Hair was present in 7 (64 per cent). Four were located in the suprasternal area, 2 along the anterior border of the sternomastoid, 2 over the thyroid cartilage, 2 in the submaxillary triangle, and 1 over the right lobe of the thyroid gland. Nine patients came to the clinic because of a mass. Two patients had adenomatous goiters, 1 toxic and 1 nontoxic, and the dermoid cysts were coincidental findings. Two patients had had operations previously, and another had a tender mass that on pathological examination revealed acute inflammation. Preoperative diagnoses included thyroglossal cyst in 2, branchial-cleft cyst in 2, cystic hygroma in 1 and lipoma in 1. All were excised without recurrence.

Tongue. One patient, a thirty-eight-year-old man, was admitted to the hospital because of an intermittent draining sinus of the posterior dorsum of the tongue that had been present for five years. He had noted the swelling beneath the tongue and chin intermittently; after the drainage of material from the dorsal aspect of the tongue, the mass had subsided. Physical examination revealed a sinus opening on the posterior dorsal aspect of the tongue from which hairs protruded. The cyst was excised. It measured 5 cm. in greatest diameter. The postoperative course was uneventful. There was no recurrence.

Head. There were 2 males and 1 female in this group. One patient had a draining sinus on admission; another had a draining mass, and in the third an attempt had previously been made to excise the mass but had been unsuccessful. The cysts were located just beneath the right ear in 1 case, in the right midmandibular area in the second and at the angle of the mouth in the third. All 3 cysts were excised. They varied in size from 1.0 to 1.5 cm. in greatest diameter. All were simple cysts; 2 contained hair, and no other tissue was found. None have recurred.

Mediastinum. There were 2 cases of mediastinal dermoids. Both patients were women, sixty and sixty-nine years of age. Both patients came to the clinic because of a mass in the neck. Roentgenograms revealed what was thought to be a substernal thyroid gland, and the preoperative diagnosis in both cases was substernal adenomatous goiter. One patient had known of the presence of the mass for fifty-five years; in the other the duration of the mass was not known. Both were simple cysts measuring 9 cm. and 14 cm., respectively, in greatest diameter. No hair was present. At operation 1 patient had all but a small portion at the base of the cyst excised. Drainage continued for a year. In the other case biopsy and drainage of the substernal mass were performed, and drainage continued for five years, when the patient was lost to follow-up study.

Presacral area. There were 8 cases of presacral dermoids in this series, 7 in females and 1 in a male. The ages ranged from seventeen to fifty-four years. On admission 4 patients had draining sinuses, 2 of whom had had previous operations for "rectal abscesses"; 2 had pain, and 2 complained of a mass. The duration of symptoms ranged from ten days to eighteen years. The cysts varied in size from 3 to 10 cm.; the size was not recorded in 2 cases. Hair was present in 2. The cysts were loculated in 2 cases. One cyst contained teeth, and another bone (Fig. 1). Six cysts (75 per cent) revealed chronic inflammation on pathological examination. Seven were excised; 2 of these healed by first intention, and the remaining 5 drained for three months to one and a half years after operation. In 1 case the cyst was incised, drained, curetted and carbolized; it drained for eight months before healing.

Ovarian Dermoid Cysts

There are no diagnostic signs or symptoms of a dermoid cyst of the ovary. These tumors are usually discovered during physical examination or while a laparotomy is being performed. They are found most frequently during the age of sexual activity.[5] This is the commonest ovarian tumor found in children.[6] The average age of the patients in the present series was forty and six-tenths years; the oldest was seventy-four, and the youngest nineteen years.

The most frequent complaint in patients with no other abdominal disease is pain in the lower abdomen, and often even this symptom is absent. In this series only 35 patients sought medical advice because of abdominal pain. It should be noted that of these 35, only 21 had a dermoid tumor alone to explain their complaints. The remaining 14 patients had other forms of pelvic disease, such as leiomyoma, salpingitis and endometriosis, which could have been responsible

for at least a part of their pain. Other complaints, such as menorrhagia, metrorrhagia, leukorrhea and urinary symptoms, were extremely rare in the absence of other pelvic disease. Two patients had pressure

FIGURE 1. *Lateral Film of the Pelvis, Showing a Mass Containing Bone and Two Teeth Indicating the Presence of a Presacral Dermoid Cyst.*

This was confirmed at operation. This case demonstrates the value of a lateral-view roentgenogram in a patient with a mass in this location. The interposition of the sacrum may obscure the bone or tooth formation on the usual antero-posterior film.

sensation in the lower portion of the abdomen, and 1 had frequency of urination.

The typical finding on physical examination is a pelvic mass. In the 41 patients who had dermoid tumors as their only pelvic pathologic change 36, or 87.8 per cent, had masses on pelvic examination, 7, or 17 per cent, had palpable abdominal masses and 3, or 7.3 per cent, had masses palpable by rectum. In the absence of complications these masses are usually nontender, smooth in contour and movable. The remaining 59 patients with dermoid cysts of the ovary had exploratory operations for other reasons, chiefly uterine fibroids. In this series 31 per cent with dermoid cysts also had leiomyomas of the uterus.

The roentgenogram may be of definite aid in the diagnosis of ovarian dermoids. The presence of teeth, for example, is indicative of either a dermoid cyst or a teratoma (Fig. 2). Calcium and bone deposits are often noted in these tumors (Fig. 3), but they must be distinguished from calcified fibroids, vesical calculi, calcified lymph nodes, phleboliths and so forth. In this series, as shown in Table 2, bone was present in 13 per cent, and teeth and calcium deposits were present in 12 per cent. Sometimes, the outline of a pelvic mass may be seen on roentgenologic examination. The mass has an outer zone of increased density because of the capsule of the cyst, and the central portion of the mass is radiolucent owing to its contents of sebaceous material.[14] The central area may also have a mottled appearance caused by the hair in the cyst (Fig. 4).

Complications

Dermoid cysts are subject to a number of complications that may alter the clinical picture consider-

FIGURE 2. *Barium-Enema Film, Showing Three Teeth, Which Are Clearly Visible in the Right Side of the Pelvis, Indicating Either a Dermoid Cyst or a Teratoma of the Ovary.*

This patient was found to have a teratoma involving the right ovary.

ably and directly affect the surgical management of these patients.

Torsion

CASE 1. A 38-year-old woman was admitted to the hospital because of generalized abdominal pain of 16 hours' duration, finally localizing in the right lower quadrant. The pain was moderately severe and constant. Anorexia was present. No nausea or vomiting was present. Eighteen months before these symptoms occurred the patient had had a similar episode, which gradually subsided. The last menstrual period had occurred ten days before admission and had been normal. The temperature was 99°F. Tenderness

in the right lower quadrant was elicited on palpation and on rectal examination, but a definite mass could not be palpated. At operation a dermoid cyst containing hair was discovered in the right ovary. The cyst measured 5 by 8 cm. and was twisted on its pedicle. The appendix was normal. The cyst was removed, and the patient made an uneventful recovery.

Case 2. A 40-year-old woman came to the clinic because of constant pain in the right lower quadrant of the abdomen for the past 24 hours. Nausea had been present, but vomiting had not occurred. Physical examination disclosed a tender mass in the right lower quadrant and a palpable mass high in the right adnexa. The white-cell count was 10,500. At laparotomy a dermoid measuring 4 by 5 cm. and containing hair and calcium was found twisted on its pedicle, and was removed. Convalescence was uneventful and the patient has had no further symptoms.

The occurrence of a twisted dermoid cyst is usually associated with acute pain, and as a result the patients may seek treatment within a few hours of onset of symptoms. Symptoms referable to the gastrointestinal and urinary tracts are absent or minimal. When these cysts occur on the right they are difficult to distinguish from acute appendicitis. The presence of a mass in the right lower quadrant or right adnexal area with a short duration of symptoms should arouse suspicion of an ovarian cyst with torsion of its pedicle.

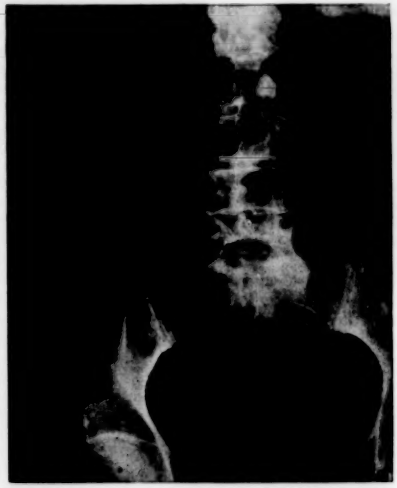

Figure 3. *Anteroposterior Film, Showing Abnormal Bone Formation Overlying the Right Iliac Bone.*
In addition the outline of the pelvic mass may be seen because of the increased density of the capsule of the cyst. A large dermoid cyst of the right ovary was removed at operation.

Perforation

In this series 2 patients had perforated cysts. In 1 case the cyst caused a pelvic abscess, and in the other chronic granulomatous peritonitis resulted.

Case 3. A 33-year-old woman was admitted to the hospital because of a mass in the lower portion of the abdomen of 2 months' duration, and pain in the left lower quadrant of 1 month's duration. The patient had no nausea, vomiting, constipation, diarrhea or genitourinary symptoms. Physical examination disclosed a large, tender, cystic mass in the left adnexal region. The uterus contained a very small fibroid. At operation an ovarian mass, 8 by 10 cm., was found. There were numerous peritoneal implants that were thought to be metastatic carcinoma. A biopsy of these nodules, however, showed only chronic granulation tissue. The ovarian mass proved to be a dermoid cyst containing hair, bone and 1 tooth. Convalescence was uneventful, and the patient has had no symptoms during 1 year of follow-up study.

Figure 4. *Dermoid Cyst of the Ovary, Showing the Mottled Appearance Caused by the Hair Within the Cyst.*
In addition bone formation in the cyst may be seen. The capsule of the cyst is well outlined.

This patient had a dermoid cyst that had perforated into the free peritoneal cavity, and later the perforation sealed itself off. The massive granulation tissue throughout the peritoneum is a typical reaction to the irritating effects of the contents of a dermoid cyst. The gross appearance at operation may suggest carcinomatosis.

Case 4. A 25-year-old woman was seen at the clinic because of pain and frequency of urination of 8 months' duration. Eight months before admission a full-term baby had been delivered without difficulty. On the 8th post-partum day pain in the lower abdomen and fever had developed. She was treated with sulfonamides and general supportive measures. All her symptoms subsided except for residual pain in the right lower quadrant and mild frequency of urination. No dysuria, hematuria or pyuria was present. Menses were regular and did not increase her pain. Physical examination disclosed a large mass in the right lower quadrant extending midway to the umbilicus. The uterus could not be delineated from this tumor by pelvic examination. At laparotomy a granulomatous mass, 11 cm. in diameter,

arising from the right ovary and attached to the terminal ileum, cecum, bladder and uterus, was found. This was carefully dissected free and a right salpingo-oöphorectomy was performed. Convalescence was uneventful. The patient has been followed for 13 years and has had no further difficulty. The cyst contained numerous strands of hair mixed with a foul-smelling, purulent material.

The cyst was unrecognized during the pregnancy, and undoubtedly the increase in intra-abdominal pressure associated with labor resulted in perforation of the dermoid. The irritating contents of the dermoid and the presence of secondary infection resulted in a large granulomatous mass. The size of the mass and its adherence to the bladder explained the urinary symptoms.

Although the occurrence of perforation is relatively rare, it is a serious complication. The contents of the cyst, when in contact with the peritoneum, produce a severe reaction. This irritation results in a granulomatous peritonitis (foreign-body, giant-cell reaction), with the occasional formation of internal and external fistulas. Adhesions are a natural sequela, and intestinal obstruction may occur. When a cyst is removed great care should be exercised to prevent soiling of the peritoneum with the cystic contents.

Pregnancy

CASE 5. A 30-year-old woman was seen at the clinic because of amenorrhea of 2 months' duration. On physical examination the uterus was slightly enlarged, and a large cystic mass was present in the cul-de-sac. The Aschheim–Zondek test was positive. To avoid a miscarriage the patient was advised to wait until gestation had progressed to 5 months and then have a laparotomy. At laparotomy the dermoid cyst was excised, and the ovary reconstructed. Proluton was given before and after operation. The cyst measured 6.5 by 8 cm. and contained hair, cartilage and calcium deposits. Convalescence was uneventful, and the patient was delivered of a full-term baby, without complications.

The presence of an ovarian dermoid cyst, by virtue of its size or location in the pelvis, constitutes a hazard for the pregnant female. The cyst may interfere mechanically with the normal process of delivery and result in a maternal or fetal death, or both. Another grave danger, as seen in this series, is rupture of the cyst during delivery, with secondary infection and peritonitis.

Parasitic cyst

CASE 6. A 61-year-old woman was seen at the clinic because of intermittent attacks of pain in the lower abdomen of 15 months' duration. Three days before admission she had had severe generalized pain, with nausea, vomiting and diarrhea. No blood was noted in the stools. On physical examination a mass was palpated abdominally and also on pelvic examination. A gastrointestinal series was normal. At laparotomy a large dermoid attached to the wall of the ileum was discovered. There was no longer any attachment to the ovary, and the tumor received its entire blood supply from the vessels in the ileum. The cyst was excised with a small portion of the wall of the ileum, and the incision in the ileum closed. The cyst measured 12 by 12 cm. and contained numerous small calcium deposits. Convalescence was uneventful.

The presence of a parasitic dermoid cyst attached to the intestine carries with it the hazards of obstruction, torsion, thrombosis of intestinal vessels and perforation of the bowel wall. Although, in the case reported above, resection of the bowel was not required, this should be done if necessary for complete removal of the cyst.

Infection. This complication was not encountered in this series of cases although secondary infection was noted after rupture of the cyst. This type of complication is rare, but when it does occur, surgical intervention is mandatory.

Malignant degeneration. Although a dermoid cyst is a benign tumor secondary malignant degeneration does occur. This malignant change occurs in the form of either sarcoma or carcinoma. Geist[10] reported malignant change in 1 per cent of these tumors. No cases of malignant degeneration were noted in this series.

Treatment. The treatment of ovarian dermoid cysts is confined to their surgical removal. They should always be removed when discovered. Since these tumors are usually benign, their removal can be accomplished with conservative technic unless malignant degeneration is present. Whenever possible, the ovary from which they arise should not be sacrificed. This is true especially in pregnant patients and in those who are in the childbearing age. At times the entire ovary may be involved by the cyst and in such a case the ovary may have to be completely removed.

Procedures used in this series were hysterectomy (38 cases), salpingo-oöphorectomy (25 cases), oöphorectomy (18 cases), excision of cyst (18 cases) and cyst excised from ileum (1 case). The large number of hysterectomies is explained by the high percentage of associated fibromyomas of the uterus (31 per cent). The remaining uteri were removed for other reasons, such as endometriosis. Extreme care should be observed in removing the cyst to avoid spilling any of its contents into the peritoneal cavity. As previously stated, these contents are extremely irritating and result in a severe, chronic granulomatous peritonitis. If soiling accidentally occurs, the contents should immediately be aspirated from the peritoneal cavity, and the area irrigated with sterile warm saline solution to remove as much of the irritant as possible. In this series no cysts were ruptured during removal. There was no operative mortality, and no evidence of recurrence has been noted.

SUMMARY

The clinical records of 146 patients with dermoid cysts are reviewed. Of this number, 31.5 per cent of the cysts were nonovarian in origin. The distribution and clinical characteristics of these nonovarian dermoid cysts are described.

The pathology, diagnosis and complications of dermoid cysts of the ovary are reviewed. Illustrative cases are reported, and their clinical significance is discussed.

References

1. Crawford, J. K., and Webster, J. P. Congenital dermoid cysts of nose. *Plast. & Reconstruct. Surg.* **9**:235-260, 1952.
2. Grabske, C. F., Jr. Dermoid cyst of midline of neck. *Arch. Otolaryngol.* **54**:183-186, 1951.
3. Randall, R. G. Congenital dermoid cysts of nasal dorsum. *J. Iowa M. Soc.* **41**:257-261, 1951.
4. New, G. B., and Erich, J. B. Dermoid cysts of head and neck. *Surg., Gynec. & Obst.* **65**:48-55, 1937.
5. Dockerty, M. B. Ovarian neoplasms: collective review of recent literature. *Internat. Abstr. Surg.* **81**:179-204, 1945.
6. Curtis, A. H. *A Textbook of Gynecology.* Fifth edition. 755 pp. Philadelphia: Saunders, 1946.
7. Blackwell, W. J., Dockerty, M. B., Masson, J. C., and Mussey, R. D. Dermoid cysts of ovary: their clinical and pathologic significance. *Am. J. Obst. & Gynec.* **51**:151-172, 1946.
8. Boyd, W. *Surgical Pathology.* Sixth edition. 858 pp. Philadelphia: Saunders, 1947.
9. Novak, E. *Gynecologic and Obstetric Pathology with Clinical and Endocrine Relations.* Third edition. 595 pp. Philadelphia: Saunders, 1952. P. 442.
10. Geist, S. H. *Ovarian Tumors.* 527 pp. New York: Hoeber, 1942.
11. Erich, J. B. Sebaceous mucous dermoid and epidermoid cysts. *Am. J. Surg.* **58**:672-677, 1940.
12. Anderson, W. A. D. *Synopsis of Pathology.* 661 pp. St. Louis: Mosby, 1942.
13. Luongo, R. A. Dermoid cyst of nasal dorsum. *Arch. Otolaryng.* **17**:755-759, 1933.
14. Robins, S. A., and White, G. Roentgen diagnosis of dermatoid cysts of ovary in absence of calcification. *Am. J. Roentgenol.* **43**: 30-34, 1940.

ACROCEPHALOSYNDACTYLISM*

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ACROCEPHALOSYNDACTYLISM is a comparatively rare congenital disease characterized by fusion of the digits and a high, peaked head, the highest point being the bregma. If the apex of the skull is posterior to the bregma the changes are not characteristic of this disease.

FIGURE 1. *Profile View of a Patient with Acrocephalosyndactylism.*

This syndrome was first recognized by Apert[1] although previous cases had been described in the literature. The bony changes of the skull were well described by Crouzon.[2] There are two extensive and well written reviews on Apert's syndrome.[3,4] In 1920 Park and Powers[5] studied all the previously published cases and summarized their views on its causation and the characteristics of the deformity. By 1932 Llambias and Mazzini[6] were able to find 48 published verified cases; they presented a case summary of each. We have not found any extensive compilation of cases since 1932. We have compiled a complete

FIGURE 2. *Typical Facies of a Patient with Acrocephalosyndactylism.*

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bibliography from 1932 to the present. However, we did not review each report because of the almost complete similarity of the case studies; furthermore, to our knowledge, there has been no new or important discovery regarding causation or therapy.[7,8]

Recently, we studied a typical case of acrocephalosyndactylism. The case is as follows:

FIGURE 3. *Deformity of the Feet in Acrocephalosyndactylism.*

CASE REPORT

An 18-year-old schoolgirl was first seen on November 27, 1953, with a chief complaint of multiple congenital defects of 18 years' duration. The patient's mother and the patient gave the history, and they stated that the patient was the second of 2 siblings. Both siblings were born at the end of 9 months' pregnancies, and they both had normal deliveries. The 1st child, a normal, healthy male infant, was precocious in all his activities, but contracted pneumonia and died at the age of 11 months. The patient was born with multiple congenital defects that particularly affected the head, the hands and the feet. After her birth, the mother had a miscarriage early in pregnancy. Since birth, the patient has had a high, cylindrical head, with bulging eyes, small curved nose and malformation of the mouth and lower jaw. In addition she has webbing, associated with malformation, of the digits. Recently, vision had begun to fail — she had formerly been the fastest reader in her class at school. She is currently a sophomore in high school and makes somewhat better than average grades. She had no other disability, except for a brownish vaginal discharge, which has been present for 3 years. The menarche occurred at 12 years of age; her periods were regular every 28 days, lasting 6 days; she has some pain on the 2d day of each period.

The past and family histories were noncontributory, as was a review of the systems.

The patient was 171 cm. (5 feet, 7½ inches) tall — somewhat taller than the normal. The hips were wide, and the shoulders narrow. The digits were webbed and malformed. The head was somewhat egg shaped. The forehead was bulging and peaked (Fig. 1). There was considerable protrusion of both eyes (Fig. 2). There was a moderate keratoconus, with rupture of the apex of the cornea on the left. The nose was small and hooked. There was improper fusion of the maxillas. The anterior portion of the palate was at approximately the right level, but fusion was poor; the posterior part of the palate was higher than the anterior and was also improperly fused. The teeth were rudimentary. The tympanic membranes were intact. The neck was very short but supple; there was no lymphadenopathy. The skin was warm and dry. The breasts were small and poorly developed. The heart was not enlarged and there were no murmurs, thrills or arrhythmias. The lungs were clear and resonant. The abdomen was very obese. The fingers and toes showed typical syndactylism (Fig. 3 and 4). The introitus was extremely small and pelvic examination was made only with great difficulty; however, no definite abnormalities were noted. The remainder of the physical examination was negative, as was fluoroscopic examination of the chest.

FIGURE 4. *Fusion of the Fingers.*

The pulse was 72, and the respirations 16. The blood pressure was 120/100.

The patient was very alert mentally, and seemed to have good intelligence. She was apparently as well adjusted to her malformation as it was possible to be.

Serologic tests for syphilis were negative. The red-cell count was 5,440,000, with a hemoglobin of 12.5 gm. per 100 cc., and the white-cell count 11,866, with 66 per cent neutrophils, 32 per cent lymphocytes, 1 per cent monocytes and 0 basophils.

The fasting blood sugar was above 130 mg. per 100 cc. One hour after a meal the value was above 180 mg. per 100 cc.

The urine was pale lemon in color and clear, with a specific gravity of 1.005, a pH of 6 and negative tests for albumin and sugar. In the spun urinary sediment occasional white blood cells saturated with epithelial cells were seen.

Hematest of the stools was negative. No ova or parasites were seen.

The vital capacity was 3.3 liters (normal, 3.9 liters). The

maximum breathing capacity was 35 liters per square meter of body surface per minute.

There was a questionably positive Master test; otherwise the electrocardiographic tracing was not remarkable.

A 6-foot film of the chest gave no evidence of cardiopulmonary disease (Fig. 5). An anteroposterior view of the skull revealed a broader than normal cranial cavity. In a posteroanterior film the calvarium had peaked configuration and seemed somewhat thinner than usual (Fig. 6). A left lateral view showed the skull to be shortened in the anteroposterior direction and lengthened in the vertical dimension. The sella turcica was definitely larger than normal (Fig. 7). The base of the skull did not have its usual configuration, owing to the shortened anteroposterior dimension. There were numerous unerupted teeth. The orbital cavities were small.

The basal metabolic rate was −12 per cent.

The Keppler–Power–Robinson water test for adrenal insufficiency was positive.

Discussion

This patient sought help because of difficulty with reading. Despite the malformation of the skull, she was an excellent reader and only in recent months had her vision begun to fail. Poor vision is a prominent complaint of patients with this disease, owing to the mechanical deformity of the skull that displaces the eyes. Restoration of good vision to our patient is a challenging problem. Tentative plans have been made for a corneal transplantation and, if possible, an orbital decompression.

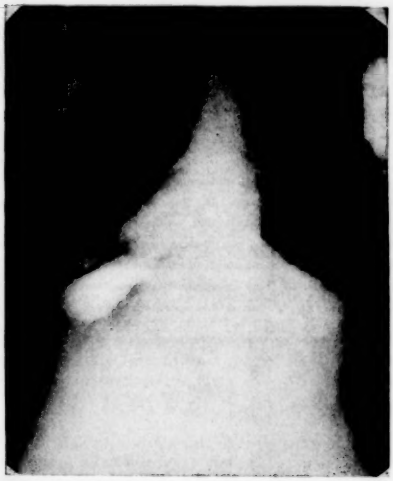

Figure 5. *Posteroanterior Film of the Chest.*

This patient's mental status is good. Through the continuing efforts of her mother, she is socially well adjusted despite her unusual appearance.

There does not seem to be any pattern of intellectual capacity among these patients. Some of the authors report average intelligence, and others retardation. In comparison with a similar number of persons without these bony defects, there are probably more mentally retarded among the cases of Apert's syndrome than among those without bony defects.[2,3,9,10]

This case gave evidence of an endocrinopathy although not all endocrine glands were involved. X-ray study of the sella turcica showed it to be somewhat enlarged. The Keppler–Power–Robinson water test for adrenal insufficiency was positive (this, of course, is not specific for hypocorticoidism but is suggestive; other conditions may produce a positive result). Two blood sugar screening tests were above normal limits — the fasting capillary blood sugar was over 130 mg. per 100 cc., and an hour after a high-carbohydrate meal the level was over 180 mg. per 100 cc. Other endocrine functions were normal.

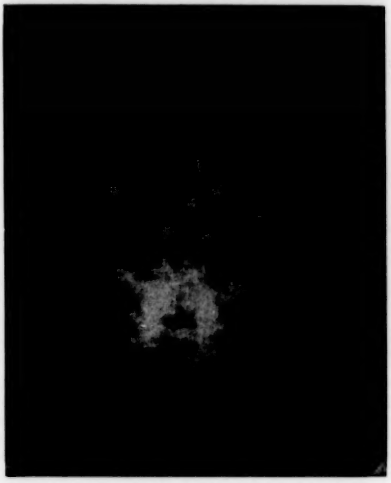

Figure 6. *Posteroanterior Film of the Skull (Note the Peaked Calvarium).*

Because of the bony deformity of the head, it was of some interest to note a minimal loss of hearing. The patient complained of occasional bouts of giddiness, which we were at a loss to explain.

Nothing in this case work-up disclosed any new clues to the cause of these malformations. The etiology was exhaustively reviewed by Park and Powers[5] (1920) and also by Cometta, Juillard and Rosselet[11] (1950), who state that this disease is hereditary in some cases and due to germ-plasm defect. Fetal infection may be a cause in some cases. Injury to the nervous system may be reflected by

abnormalities in osseous development. Pituitary malfunction has been suggested. Tuberculosis, toxoplasmosis and other chronic diseases have been suspected but never proved.

It is of interest to reiterate the conclusion of Park and Powers[5] about the extremities: there is bone involvement as well as soft tissue; the more distal parts are most maldeveloped, the arms are more deformed than the eyes, and the malformations are bilateral and symmetrical; the malformations are not new formations.

FIGURE 7. *Left Lateral View of the Skull (Note the Size of the Sella Turcica).*

The skull in these cases is very high, and in most cases the highest point is the anterior fontanel although there is some variation in this. The cranial vault looks somewhat peaked like a shed roof in the anteroposterior roentgenogram. The skull is broad. In profile the posterior surface of the skull is very flat. Park and Powers[5] state that "eyeballs were set obliquely in such manner that their horizontal axes passed from within slightly downward." Strabismus may be present.

In general this case presents the problem of making a continuing effort to keep the patient adapted and adjusted to her environment in spite of her many congenital defects.

SUMMARY

A case of Apert's syndrome of acrocephalosyndactylism is presented. The various forms of involvement are discussed. The obscurity of the etiology is reiterated.

REFERENCES

1. Apert. A propos du procès-verbal: acrocéphalosyndactylie. *Bull. et mém. Soc. méd. d. hôp. de Paris* **67**:1669-1672, 1923.
2. Couzon, O. Sur la dysostose cranio-faciale héréditaire et sur les rapports avec l'acrocéphalo-syndactylie. *Bull. et mém. Soc. méd. d. hôp. de Paris* **68**:1568-1574, 1932.
3. Apert, Tixer, Huc and Kemorgant. Nouvelle observation d'acrocéphalosyndactylie. *Bull. et mém. Soc. méd. d. hôp. de Paris* **67**: 1672-1675, 1923.
4. Euzière, J., Viallefont, H., Vidal, J., and Zakhajm. Acrocéphalosyndactylie avec microcéphalie, ptosis et infantilisme: paraplégie spasmodique ainsi surajoutée. *Arch. Soc. d. sc. méd. et biol. de Montpellier* **14**:110-119, 1933.
5. Park, E. A., and Powers, G. F. Acrocephaly and scaphocephaly with symmetrically distributed malformations of extremities, study of so-called "acrocephalosyndactylism." *Am. J. Dis. Child.* **20**:235, 1920.
6. Llambias, J., and Mazzini, O. Enfermedad de Apert, acrocéfalosindactilia: estudio clínico anátomopatológico y radiográfico. *Semana méd.* **39**:1575-1608, 1932.
7. Marischnig, E., and Thalhammer, O. Akrocephalosyndaktylie: Erörterung der Genese vom Gesichtspunkt der Embryopathie. *Helvet. paediat. acta* **7**:257-271, 1952.
8. Plucinski, K. Acrocephalosyndactylism. *Ginek. polska* **11**:661-676, 1932.
9. Cohn, B. N. E. True oxycephaly with syndactylism: case report. *Am. J. Surg.* **68**:93-99, 1945.
10. Johnstone, G. C. Case of acrocephalo-syndactylism. *Lancet* **2**:15, 1932.
11. Cometta, F., Juillard, E., and Rouselet, P. A propos d'un cas d'acrocéphalosyndactylie. *Ophthalmologica* **120**:72-78, 1950.

FURADANTIN IN URINARY-TRACT INFECTIONS*

Clinical and Laboratory Studies

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A NUMBER of infections encountered in urologic practice, primarily those due to *Proteus vulgaris* and *Pseudomonas aeruginosa,* are resistant to many antibiotic and chemotherapeutic agents. Furadantin,** a more recent chemotherapeutic agent, has shown considerable promise as a urinary antiseptic.[1-10] According to available reports, this drug is effective in infections due to both gram-positive and gram-negative organisms, including *P. vulgaris.* However, Furadantin has not been sufficiently evaluated to permit definitive conclusions regarding its antibacterial spectrum, long-range clinical effectiveness and patient tolerance. The present paper concerns a further study of the drug as a urinary antiseptic. Findings are summarized and correlated with previously reported clinical studies.

DESCRIPTION AND DOSAGE

Furadantin is the first of the nitrofuran derivatives to be released for systemic use. It is listed in the *New and Nonofficial Remedies* as nitrofurantoin, and the structural formula is given by Norfleet et al.[1] This chemotherapeutic agent is rapidly excreted by the kidneys, producing low blood and high urine levels. Since 30 to 45 per cent is excreted,[11] it is particularly suitable for combating infections of the urinary tract.

The dosage prescribed ranged from 300 mg. to 800 mg. daily (4-14 mg. per kilogram of body weight per day), depending on the patient's weight, the severity of infection and tolerance to the drug. It was found desirable to give Furadantin with meals to prevent or reduce nausea. In most cases the period of treatment was seven to ten days.

RESPONSE

The clinical and bacteriologic response of 49 urinary-tract infections is summarized in Table 1. (The infections appeared in 45 patients, 4 of whom received a second complete course of therapy four months or more after the first.) Clinical response was evaluated on the basis of the symptomatic improvement and the clearing of the pyuria. (Cases of apparent abacterial pyuria are not included in this report.) Microscopical examination of fresh urine for cell count was made frequently. Bacteriologic response was determined by periodic urine culture. Follow-up studies for evidence of relapse or reinfection were carried out for at least three months. It is to be noted that most of the cases treated had failed to respond to therapy with other antibiotics or chemotherapeutic agents.

Acute and subacute as well as postoperative infections appeared to respond well to Furadantin therapy. Six of the 13 cases in this group appeared to be cured, and 6 of the remainder showed marked improvement with no relapses. However, since such infections may be self-clearing, these results must be interpreted with caution.

Of 36 chronic infections treated, 30 showed symptomatic improvement. Frequently, patients reported symptomatic improvement within twenty-four hours of the beginning of treatment. The infecting organisms were at least temporarily cleared in 22 of the 36 infections. Since bacterial infections in such cases are almost never self-clearing,[12] the observed responses may be attributed to the Furadantin. During the period of study 12 of the 22 chronic infections temporarily cleared relapsed with the same or with another infecting organism. This observation, together with the fact that only 1 of the 36 chronic infections appeared to be permanently cured after therapy, emphasizes the fact that no antibiotic or chemotherapeutic agent can ordinarily be expected to render a permanent cure in conditions in which uncorrected neurogenic or obstructive uropathies — or both — exist. Neurogenically affected urinary bladders and urethral stricture are common examples.

A total of 7 infections failed to respond clinically to therapy. *Ps. aeruginosa* was isolated from 4 of these patients. One case involving *Ps. aeruginosa* and three other micro-organisms showed clinical improvement and bacteriologic clearing of all other organisms.

Bacteriologic responses by 47 organisms appearing in the chronic infections listed in Table 1 are summarized in Table 2. Approximately 53 per cent of the organisms encountered in this series appeared to be permanently cleared. Recurrence of infection due to organisms of the same species was observed in 7 cases. Half or more of the strains of *Esch. coli, Aerobacter aerogenes,* species of proteus, *Streptococcus faecalis* and species of micrococcus were cleared, but none of the strains of *Ps. aeruginosa* encountered were affected.

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**Available from Eaton Laboratories, Incorporated, Norwich, New York.

Reactions

Sixty patients with chronic or acute urinary-tract infections received Furadantin therapy. Of these, 15 (25 per cent) reported reactions after the first course of therapy (Table 3).

The reactions were chiefly mild gastrointestinal disturbances. In 9 cases therapy was continued either at the same or in a reduced dosage. It is interesting that 11 of the 15 reactions were reported by females although equal numbers of males and females were included in the group. Also, 4 of the 6 cases in which treatment was discontinued because of reactions were in females. Among 4 patients reporting reactions to dosages of 6.9 mg. or less per kilogram of body weight per day 1 (R.A.) had received only part of the prescribed daily dosage when therapy was discontinued, and 2 had displayed poor tolerance to other drugs. Therefore, the high proportion of patients on 4 to 6.9 mg. per kilogram of body weight per day that reported reactions must be interpreted with caution. Details of the two most severe reactions reported by patients during the first course of therapy are as follows:

A.P., a 35-year-old woman, had had a nephrectomy 9 years previously for pyonephrosis. In March, 1954, urinalyses showed the presence of pyuria. A strain of *Gaffkya tetragena* sensitive to Furadantin and erythromycin and resistant to penicillin, chlortetracycline and oxytetracycline was isolated. A course of 150 mg. of Furadantin 4 times a day was initiated. After 10 days of treatment the patient complained of malaise, chills, nausea and vomiting and had a temperature of 103°F. Fever and acute symptoms lasted 40 hours after Furadantin was discontinued. Five days later 2 doses of 150 mg. again promptly caused elevation of temperature to 103°F., with the same symptoms followed by similar subsidence after medication was stopped. Complete blood counts were those of normal health. Cultures of the urine showed no bacteria to be present.

Table 1. *Clinical and Bacteriologic Response to Furadantin Therapy.*

Patient	Sex	Age	Specific Diagnosis	Clinical Response	Infecting Organism	Bacterial Response as Judged from Follow-up Culture
		yr.				
Chronic cystitis:						
M.L.	M	51	Chronic urethrocystitis	Great improvement	Enterococcus	Infection cleared
T.M.	M	70	Chronic urethrocystitis	Improvement	*Micrococcus pyogenes* (var. *aureus*)	Infection cleared
E.A.	M	76	Chronic cystitis; diverticulum.	Improvement	Proteus	Infection cleared
J.Z.	M	68	Chronic interstitial cystitis	Improvement	*Esch. coli* & proteus	Relapse (due to proteus) in 3 mo.
T.N.	F	52	Chronic interstitial cystitis	Improvement	*Esch. coli*	Relapse (due to *Esch. coli*) in 3 mo.
M.S.	F	32	Chronic urethrocystitis	Improvement	Proteus	Relapse (due to proteus) in 5 mo.
W.C.	M	75	Chronic cystitis; carcinoma of prostate.	Improvement	Proteus	Organism replaced by *M. aureus*
E.C.	F	68	Chronic *Escherichia coli* urethrocystitis	Improvement	*Esch. coli*	Relapse (due to *Esch. coli*) in 5 mo.
M.S.	F	74	Chronic cystitis; neurogenic bladder.	Improvement	*Aerobacter aerogenes*	Relapse (due to proteus & enterococcus) in 4 mo.
M.M.	M	74	Chronic cystic cystitis	Improvement	*A. aerogenes* & enterococcus	*A. aerogenes* not cleared
M.V.	F	41	Chronic low-grade cystitis & spastic paraplegia	Improvement	*M. pyogenes* (var. *aureus*)	Infection not cleared
				Improvement	*Esch. coli*	Infection not cleared
H.T.	F	39	Chronic urethrocystitis	Failure	*A. aerogenes*	Infection not cleared
M.V.	F	34	Chronic urethrocystitis	Failure	*M. pyogenes* (var. *aureus*)	Infection not cleared
Chronic pyelonephritis:						
H.E.	F	48	Chronic pyelonephritis	Improvement	*Esch. coli*	Relapse (due to *Esch. coli*) in 7 mo.
S.I.	F	23	Chronic pyelonephritis; double rt. kidney.	Improvement	Proteus	Relapse (due to proteus) in 6 mo.
S.C.	F	50	Chronic pyelonephritis	Improvement	*A. aerogenes*, *Esch. coli*, pseudomonas	All cleared except pseudomonas
C.A.	F	76	Chronic pyelonephritis; cystitis.	Slight improvement	Proteus	Relapse (due to *Klebsiella pneumoniae*) in 1 mo.
W.B.	F	29	Chronic pyelonephritis; urethral stricture.	Improvement	Proteus	Infection not cleared
S.P.	M	44	Chronic pyelonephritis	Failure	Pseudomonas & *M. pyogenes* (var. *aureus*)	Pseudomonas persisted
				Failure	Pseudomonas & *Esch. coli*	Pseudomonas persisted
E.R.	M	50	Chronic pyelonephritis	Failure	Pseudomonas	Infection not cleared
Chronic prostatitis:						
K.T.	M	70	Chronic urethroprostatitis	Improvement	*Esch. coli* & proteus	Infection with both organisms cleared
H.D.	M	43	Chronic urethroprostatitis	Improvement	*A. aerogenes*	Infection cleared

R.K., a 44-year-old man, had chronic cystitis with alkaline incrustations. In July, 1954, he complained of burning and frequency with nocturia (twice). Furadantin was prescribed for a strain of *Ps. aeruginosa* that was resistant by in vitro tests to penicillin, streptomycin, chlortetracycline, oxytetracycline, chloramphenicol, Furadantin and tetracycline. At the beginning of treatment he complained of slight nausea. After 5 days of treatment 4 or 5 pus cells per high-power field were present in the fresh, uncentrifuged urine. Furadantin dosage was increased to 200 mg. 4 times a day. Four days later urticaria and angioneurotic edema developed. Furadantin therapy was discontinued; the patient was given 400 units of ACTH. The symptoms subsided in about 36 hours.

TABLE 1 *(Concluded).*

PATIENT	SEX	AGE	SPECIFIC DIAGNOSIS	CLINICAL RESPONSE	INFECTING ORGANISM	BACTERIAL RESPONSE AS JUDGED FROM FOLLOW-UP CULTURE
		yr.				
Chronic prostatitis:						
T.G.	M	50	Chronic prostatitis; urethral stricture.	Improvement	2 enterococci	Infection with both organisms cleared
B.G.	M	39	Chronic urethroprostatitis	Improvement	Enterococcus	Infection cleared
M.C.	M	48	Chronic prostatitis; ureteral & urethral strictures.	Slight improvement	Proteus	Organism replaced by *A. aerogenes*
				Improvement	*A. aerogenes*	Infection cleared
M.N.	M	23	Chronic prostatitis	Improvement	*A. aerogenes*	Relapse (due to *A. aerogenes* & enterococcus) in 2½ mo.
J.S.	M	60	Chronic prostatitis	Improvement	*M. albus*	Infection not cleared
J.D.	M	49	Chronic prostatitis; nephrolithiasis.	Improvement	*A. aerogenes*	Infection not cleared
C.S.	M	55	Chronic urethroprostatitis	Improvement	Enterococcus	Infection not cleared
D.M.	M	43	Chronic prostatic vesiculitis	Failure	*Esch. coli* & pseudomonas	Infection not cleared
Other chronic infections:						
J.E.	M	49	Chronic diverticulum of bladder	Cure	*A. aerogenes*	Infection cleared
W.W.	M	54	Chronic urethritis	Improvement	*M. albus* & enterococcus	Organism replaced by pseudomonas
R.F.	M	73	Chronic urethritis; urethral stricture.	Improvement	Enterococcus	Relapse (due to proteus and *A. aerogenes)* in 3 mo.
Acute & subacute infections:						
G.C.	F	37	Acute cystitis	Cure	*A. aerogenes*	Infection cleared
E.S.	F	40	Acute cystitis	Cure	*Esch. coli*	Infection cleared
L.C.	F	24	Subacute cystitis	Improvement	*A. aerogenes*	Relapse (due to *Esch. coli)*
				Improvement	*Esch. coli*	Infection not cleared
J.B.	F	36	Acute urethritis	Cure	*Esch. coli*	Infection cleared
N.L.	M	24	Subacute prostatitis	Cure	*A. aerogenes*	Infection cleared
L.R.	F	43	Pseudomembranous trigonitis	Great improvement	*Esch. coli*	Infection cleared
C.W.	M	54	Subacute urethroprostatitis	Failure	Enterococcus	Infection not cleared
Postoperative infections:						
G.L.	M	54	Bladder-tumor operation.	Cure	*Esch. coli*	Infection cleared
A.P.	F	35	Unilateral nephrectomy	Cure	*Gaffkya tetragena*	Infection cleared
N.P.	F	18	Postoperative urethrocystitis	Improvement	*A. aerogenes*	Infection cleared
F.E.	F	54	Removal of urethral polyp; subacute cystitis.	Great improvement	*A. aerogenes*	Relapse (due to enterococcus) in 4 mo.
D.J.	F	45	Postoperative ureterocele; urethrocystitis.	Improvement	*Esch. coli*	Relapse in 4 mo.

Of the 11 patients receiving more than one course of therapy 4 showed a decreased tolerance to the drug. These 4 cases are described in detail below:

M.S., a 32-year-old woman, had chronic recurrent urethrocystitis and partial paraplegia. In April, 1953, the uncentrifuged urine contained 6 to 8 pus cells per high-power field. *P. vulgaris* was isolated. The patient received 100 mg. of Furadantin 4 times a day for 10 days. No reactions occurred. She improved, and the urine cleared. In November a recurrence of a proteus infection was again treated with 100 mg. of Furadantin 4 times a day. The organism was sensitive to Furadantin and chloramphenicol and resistant to penicillin, streptomycin, chlortetracycline and oxytetracycline. During the 7th day of treatment joint pains and nausea developed, and the temperature rose to 99.4°F. About 24 hours after therapy was discontinued the symptoms subsided. In July, 1954, a proteus infection resistant to penicillin, streptomycin, chlortetracycline, chloramphenicol, oxytetracycline, tetracycline and Furadantin was observed. Treatment with Furadantin, 100 mg. 4 times a day, was resumed. After 2 days of therapy joint pains developed. Symptoms again subsided about 24 hours after therapy was discontinued.

E.C., a 68-year-old woman, had chronic *Esch. coli* infection of 12 years' duration. In October, 1953, low-grade pyuria due to *Esch. coli* was observed. Furadantin, 100 mg. 4 times a day for 10 days, was well tolerated except for slight anorexia. Urinary symptoms subsided. Urine cultures were sterile. In March, 1954, a recurrent infection, treated with 200 mg. of Furadantin 4 times a day for 7 days, showed clinical improvement. No reactions developed. However, *Esch. coli* was again recovered from the urine. Treatment

with Furadantin was instituted. Nausea, emesis and 1° elevation of temperature followed the 3d dose. Symptoms subsided when treatment was discontinued. Four days later a single dose of 200 mg. caused nausea and fever of about 24 hours' duration that, in turn, was followed by a feeling of generalized fatigue.

M.W., a 41-year-old woman, had low-grade cystitis and partial paraplegia. In February, 1954, urinalysis demonstrated 4 to 6 pus cells per high-power field in the fresh,

TABLE 2. *Bacteriologic Responses in Chronic Urinary Infections.*

ORGANISM	NO. OF STRAINS ISOLATED	NO. CLEARED INITIALLY	NO. CLEARED FOR 4 TO 7 MO.
Esch. coli	9	7	4
A. aerogenes	9	6	5
Species of proteus	10	9	6
Ps. aeruginosa	5		
Enterococcus	8	7	7
Species of micrococcus	6	3	3
Totals	47	32	25

uncentrifuged urine. *G. tetragena* was isolated. The patient was given 150 mg. of Furadantin 4 times a day. Symptomatic improvement was observed, and the urine cleared bacteriologically. No reactions were reported. In June 150 mg. of Furadantin 4 times a day was once more prescribed for treatment of an infection due to an *Esch. coli* sensitive to streptomycin, chloramphenicol and tetracycline and resistant to penicillin, chlortetracycline, oxytetracycline, Furadantin and erythromycin. Therapy was discontinued because of nausea. The patient had previously tolerated drugs well.

A.K., a 73-year-old man with benign prostatic hypertrophy, in December, 1953, had 3 or 4 pus cells per high-power field in the fresh sediment. A species of proteus sensitive to chlortetracycline, chloramphenicol, oxytetracycline and Furadantin and resistant to penicillin and streptomycin was isolated. Furadantin, 150 mg. 4 times a day, was given for 10 days. Some clinical improvement was observed, and the drug was well tolerated. In August, 1954, a recurrence of infection with a species of proteus having the same in vitro sensitivity pattern as the organism isolated in the previous December was treated with 100 mg. of Furadantin 4 times a day. After 7 days of treatment the patient discontinued the drug because of nausea and severe malaise.

DISCUSSION

Among the published clinical studies on the use of Furadantin in the treatment of urinary-tract infections,[1-10] three[2-4] give separate data on its effectiveness against different species of organisms in chronic infections. The difference between the responses of acute and chronic cases is well illustrated by the data of Friedgood et al.,[5,6] who, in a series of 108 patients, obtained bacteriologic clearing with Furadantin in 85 per cent of the acute and 55 per cent of the chronic infections. Essentially the same proportions of bacteriologic clearings were observed in the present study. Thus, data on the combined responses of chronic and acute infections must be interpreted with caution.

Published data,[2-4] together with those presented in this paper on the bacteriologic responses of chronic urinary-tract infections, are summarized in Table 4. Since the number of infections by each of the groups of organisms was quite small, comparisons were made with their relative responses in vitro. The relative sensitivity of these groups of organisms as determined by the tube-dilution method[2,7,11] compared favorably with the results shown in Table 4 with two exceptions: species of proteus appeared more resistant and species of micrococcus more sensitive in vitro. Thus, the responses of the different groups of organisms shown in Table 4 may be regarded as a reliable preliminary estimate. According to these data Furadantin appears to be of value in the treatment of urinary-tract infections due to the bacteria normally encountered, except those due to *Ps. aeruginosa*. Further studies on responses in chronic urinary-tract infections will have to be conducted to determine more accurately the proportions of the different groups of organisms responding to Furadantin.

TABLE 3. *Reactions Reported among 60 Patients Receiving Single Course of Furadantin Therapy.*

PATIENT	SEX	AGE	DOSAGE	REACTION	COMMENT
		yr.	mg./kg./day		
Gastrointestinal disturbances:					
R.A.	F	70	4.9	Nausea	Therapy discontinued
T.N.	F	52	6.4	Mild heartburn; pain in stomach; tiredness.	Therapy continued for 10 days
W.B.	F	29	6.5	Some nausea	Therapy continued for 7 days
M.F.	F	60	6.5	Some diarrhea & depression	Therapy continued for 10 days
V.G.	M	60	7.0	Marked nausea	Therapy discontinued
J.E.	M	47	7.8	Some nausea initially	Therapy continued for 20 days
H.T.	F	39	8.8	Nausea & bloating after 4 days	Therapy discontinued
H.D.	M	43	8.8	Some nausea	Therapy continued for 7 days
N.P.	F	18	9.1	Nausea after 5 days	Therapy discontinued
E.S.	F	40	10.2	Slight nausea	Therapy continued for 16 days
S.I.	F	23	10.5	Some nausea	No reaction when dosage reduced to 5.3 mg. per kg.
S.C.	F	50	12.0	Some nausea initially	Therapy continued for 50 days
Other reactions:					
M.V.	F	34	10.7 7.1	General pruritus Tolerated better; hands stiff.	No medication tolerated well; possible hypopituitarism.
A.P.	F	35	10.2	Temperature 103° F.; nausea, chills & vomiting on 10th day of therapy.	Therapy discontinued; same reactions after single doses of 150 mg. 5 & 10 days later.
R.K.	M	44	8.8 11.7	Slight nausea at onset Urticaria; angioneurotic edema.	Therapy discontinued after total of 9 days

There is general agreement among the various reports on clinical trials of Furadantin[1-10] that the prime reaction to its ingestion is nausea, occasionally accompanied by emesis. Careful studies by Mintzer et al.[2] indicate that dosages of 5 to 7 mg. per kilogram of body weight per day produce such a reaction in about 3 per cent of the cases (2 out of 59) whereas dosages

of 10 to 12 mg. cause reactions in about 28 per cent of the patients (6 cases of nausea and 1 of emesis among 25 patients).

Schatten and Persky[3] reported 3 reactions in 67 cases (4.5 per cent) on dosages of 7 mg. per kilogram of body weight per day. Two other publications[1,10] described 7 reactions in 50 cases (14 per cent) and 2 reactions in 15 cases (13.3 per cent) on dosages of 7 to 9 and 5 to 8 mg. respectively. In the present study 9 of 45 patients (20 per cent) receiving 9.9 mg. or less per kilogram of body weight per day and 6 of 15 patients (40 per cent) receiving 10 to 15 mg. reported reactions. Considerably higher reaction rates followed dosages of 5 to 7 mg. per kilogram of body weight per day, according to two publications: Hasen and Moore[8] described about 29 per cent of reactions among about 103 patients, and Abrams and Prophete[4] mentioned 5 reactions among 29 patients (42 per cent). With the exception of these two papers the available reports indicate a sharp, progressive increase in the frequency of reactions with dosages over 7 mg. of Furadantin per kilogram of body weight per day. This is in accord with the manufacturer's recommendations. However, occasional reactions are reported even on regimens well below the prescribed dosage.

Other gastrointestinal disturbances, including diarrhea and heartburn, occasionally appeared to be associated with Furadantin treatment among our patients. In 2 cases severe gastrointestinal disturbances were accompanied by elevated temperatures and in 1 subject by joint pains. Occasional reactions of headache and dizziness were reported.

The following evidence suggesting possible sensitization has been reported: a case of maculopapular eruptions,[7] 1 of urticaria[5] and 1 of papular exanthema.[9] In the present study a case of urticaria with angioneurotic edema appears to have been associated with the drug, and 4 out of 11 patients receiving repeated courses of treatment appear to have developed a decreased tolerance. In view of the elusive nature of allergic phenomena no conclusions about the sensitizing properties of Furadantin can be drawn from the available evidence. It will be necessary to carry out controlled studies to determine whether true sensitization can occur.

Summary

Symptomatic improvement was effected by Furadantin therapy in 30 of 36 cases of chronic urinary-tract infections, and in 12 of 13 cases of acute, subacute and postoperative infections.

Twenty-five of the 47 organisms isolated from chronic urinary infections were cleared without recurrence during the period of study, and an additional 7 organisms were cleared for two and a half to seven months after cessation of treatment. Seven of the 10 organisms encountered in acute, subacute and postoperative infections disappeared after such treatment. The majority of the strains of *Escherichia coli, Aerobacter aerogenes,* species of proteus, *Streptococcus faecalis* and species of micrococcus encountered in chronic infections were cleared by Furadantin. None of the strains of *Pseudomonas aeruginosa* encountered were cleared.

On a dosage schedule of 4 to 12 mg. per kilogram of body weight per day 15 of 60 patients reported reactions to the drug. Almost all of these were disturbances of the gastrointestinal tract.

Four of 11 patients receiving a second course demonstrated decreased tolerance to the drug.

A review of the literature on bacteriologic responses and reactions to Furadantin therapy of urinary-tract infections is presented.

Table 4. *Bacteriologic Responses of Chronic Urinary-Tract Infections.*

Source of Information	Organism Involved	Total Infections Reported	No. of Infections Cleared
Mintzer et al.,[2] Schatten & Persky[3] Abrams & Prophete[4] & present report	*Esch. coli*	23	17(74%)
Mintzer et al.,[2] Schatten & Persky,[3] Abrams & Prophete[4] & present report	*A. aerogenes*	21	10(48%)
Schatten & Persky[3]	Paracolon bacillus	3	2 —
Schatten & Persky,[3] Abrams & Prophete[4] & present report	Species of proteus	27	18(67%)
Abrams & Prophete[4] & present report	*Ps. aeruginosa*	8	0 —
Mintzer et al.,[2] Schatten & Persky[3] & present report	Enterococcus	14	12(86%)
Schatten & Persky[3] & present report	Species of micrococcus	17	6(35%)
Totals		113	65(58%)

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References

1. Norfleet, C. M., Jr., Beamer, P. R., and Carpenter, H. M. Furadantin in infections of genito-urinary tract. *Tr. Southeast. Sect. Am. Urol. A.* **16**:26-33, 1952.
2. Mintzer, S., Kadison, E. R., Shlaes, W. H., and Felsenfeld, O. Treatment of urinary tract infections with new antibacterial nitrofuran. *Antibiotics & Chemother.* **3**:151-157, 1953.
3. Schatten, W. E., and Persky, L. Furadantin in therapy of genito-urinary tract infections. *Am. J. Surg.* **86**:720-722, 1953.
4. Abrams, M., and Prophete, B. Furadantin: use in treatment of urinary tract infections. *Missouri Med.* **51**:280-282, 1954.
5. Fredgood, C. E., and Ripstein, C. B. Furadantin in treatment of infections due to *B. proteus. Bull. New York Acad. Med.* **30**:322, 1954.
6. *Idem.* Furadantin in treatment of infections due to antibiotic resistant organisms. *Internat. Rec. M. & G. P. Clin.* **167**:218, 1954.
7. Carroll, G., and Brennan, R. V. Furadantin. *J. Urol.* **71**:650-654, 1954.
8. Hasen, H. B., and Moore, T. D. Nitrofurantoin: study in vitro and in vivo in one hundred cases of urinary infections. *J. Am. Med.* **155**:1470-1473, 1954.
9. Jensen, H. B., Lund, J., and Poulsen, P. E. Furadantin et nyt kemoterapeutikum mod urinvejsinfektioner. *Ugeskr. f. laeger* **116**: 53-56, 1954.
10. Rubin, S. W., Ibsen, M., and Goldstein, A. E. Furadantin in urinary tract infections: preliminary report, with use of Furadantin diagnostic tablets. *Bull. Dade Co. M. A.* **24** (No. 4):29, 1954.
11. Beutner, E. H., Petronio, J. J., Lind, H. E., Tralton, H. M., and Correia-Branco, M. Nitrofurantoin, rational *in vitro* bacterial sensitivity testing. *Antibiotics Annual 1954-1955* (in press).
12. Stenderup, A., Kissmeyer-Nielson, F., and Linnet-Jepsen, P. Chemotherapy of infections of urinary tract. *Acta med. Scandinav.* **144**:124-136, 1952.

EFFECT OF KIMMELSTIEL—WILSON SYNDROME ON INSULIN REQUIREMENTS IN DIABETES*

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A LESION of the renal glomeruli associated clinically with diabetes, albuminuria, hypertension and edema of the nephrotic type was described by Kimmelstiel and Wilson[1] in 1936. The clinical features of the syndrome have been well defined.[2,3] Pathologically, the "nodular" glomerular lesion is generally accepted as specific.[2] The pathogenesis of this disease is poorly understood. Rich, Berthrong and Bennett[4] described renal lesions resembling those of intercapillary glomerulosclerosis in rabbits given intramuscular injections of cortisone. Friedenwald[5] presented clinical and experimental evidence that relative adrenal hyperfunction with possible associated vitamin B_{12} deficiency is causally related to the development of both glomerular and retinal lesions.

Zubrod et al.[6] have suggested that Kimmelstiel–Wilson lesions of the kidney are associated with a specific type of diabetes characterized by amelioration of the severity of the diabetes and infrequent occurrence of acidosis.[6] Our interest was drawn to this particular study by the autopsy finding, during an eight-month period, of Kimmelstiel–Wilson renal lesions in 2 of 3 patients whose deaths were associated with diabetic acidosis. Furthermore, during this period, in 5 patients followed in the clinic who presented the classic clinical syndrome of Kimmelstiel and Wilson[1] detailed dietary histories revealed a marked decrease in food intake coinciding with the onset or progression of the clinical features of this disease. Insulin requirements were altered to variable degrees. Only 1 of these 5 patients was examined post mortem, and in this patient the kidney lesions described by Kimmelstiel and Wilson[1] were demonstrated.

In view of these experiences, a review of autopsy cases with diabetes mellitus at the Boston City Hospital was undertaken to learn whether alterations in insulin requirement were related to the renal lesions per se, to certain clinical features or to a specific type of diabetes.

METHODS

The clinical and pathological records of 375 patients with diabetes mellitus examined at autopsy during the period 1940 - 1952 were reviewed. Of this group there were 138 patients with the Kimmelstiel–Wilson renal lesions and 237 without the lesions. To evaluate the clinical courses of these patients, the study was limited to those who had had diabetes for three years or more, had been on insulin for at least eight consecutive months, and whose clinical records were sufficiently detailed to yield all the necessary data. There were 106 such cases, which were divided on the basis of the pathological examination into two groups: those with (54) and those without (52) the lesions. The amount of insulin received during a basal and preterminal period was recorded. The basal period was taken to be the mid-point in the course of the diabetes when the patient was free of acute stress. The preterminal period represented the period of several months just before the terminal admission. Changes in insulin requirements were recorded without reference to clinical improvement of the diabetes.

The clinical syndrome included cases of edema, albuminuria and hypertension beginning before the terminal period and, for the purposes of clinical comparison, included cases both with and without proved Kimmelstiel–Wilson renal lesions. The edema was usually progressive and often nephrotic. Consistent albuminuria was often present to a considerable de-

TABLE 1. *Data in Patients with and without Kimmelstiel–Wilson Lesions.*

GROUP	TOTAL NUMBER	SEX		AVERAGE AGE AT DEATH	DURATION OF DIABETES	INSULIN REQUIREMENT		PATIENTS WITH ACIDOSIS	EPISODES OF ACIDOSIS	PATIENTS WITH ACIDOSIS ASSOCIATED WITH TERMINAL ADMISSION
		MALES	FEMALES			AVERAGE BASAL	AVERAGE PRETERMINAL			
				yr.	yr.	units	units			
Patient with lesions	54	14	40	61	13	27	25	14	25	8
Patient without lesions	52	25	27	62	11	29	27	9	11	4

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gree. Hypertension was variable; a few patients showed only slightly elevated blood pressure.

In addition to this clinical syndrome, certain clinical features were analyzed on individual bases to evaluate their influence, if any, on changes in insulin requirement. Nitrogen retention was considered to be present if there was a persistent elevation of nonprotein nitrogen above 60 mg. or of blood urea nitrogen above 35 mg. per 100 cc. When pitting edema above a trace was present and not due to local causes, the case was classified under the heading of edema. When a trace or more of albumin was found in the urine on more than one occasion, the case was grouped under albuminuria. For classification nitrogen retention, edema and albuminuria had to be present before the terminal admission.

Diabetic acidosis was diagnosed on the basis of a lowered carbon dioxide combining power, high blood sugar, marked glycosuria and acetonuria. The total dose of insulin (at least 250 units) administered during the period of acetonuria had to exceed greatly the requirement before or after the episode or the diagnosis of diabetic acidosis was not made. In this way, acidosis from other causes, such as uremia, could be more definitely excluded.

Blood sugar determinations were not included in the tabulations because in a number of cases it was not possible to be certain that the patient was free of stress. Because of the frequent occurrence of edema, often massive, conclusions concerning gain or loss of body tissue would not have been valid. Dietary data were not included in these studies owing to the inadequacy of the clinical records in this regard and the lack of autopsy data in patients followed clinically on whom detailed dietary information was available.

Kidney sections were reviewed without knowledge of the clinical data, and those showing Kimmelstiel–Wilson lesions, not previously grouped, were classified according to the degree of involvement. The pathological description of some of the cases has been reported elsewhere.[7]

Results

The two groups of patients studied, those with and those without Kimmelstiel–Wilson lesions, were comparable in age at death, duration of diabetes and insulin requirement during the basal and preterminal periods (Table 1). There was a slight decrease (2 units) in the average insulin requirement from the basal to the preterminal period in both groups. Table 2 shows the changes in insulin requirement on which the average was obtained. Of the group with Kimmelstiel–Wilson lesions, 27.8 per cent had an increase in insulin requirement, compared with 25 per cent of the group without the lesions. Insulin requirements decreased in 40.7 per cent of patients with and in 37 per cent of those without Kimmelstiel–Wilson lesions. The two groups were therefore quite similar in the proportion of patients with increases and decreases in insulin requirement. The actual insulin dosage received by the two groups during the basal and preterminal periods was also similar.

Fifteen patients required no insulin before the terminal admission, 5 with proved Kimmelstiel–Wilson lesions and 10 without the lesions (Table 3). Three

TABLE 2. *Changes in Insulin Requirement.*

Insulin Requirement	Patients with Kimmelstiel–Wilson Lesions				Patients without Kimmelstiel–Wilson Lesions			
	Increased requirement	Decreased requirement	Same requirement	Total	Increased requirement	Decreased requirement	Same requirement	Total
units/day								
	15(27.8%)	22(40.7%)	17(31.5%)	54	13(25%)	19(37%)	20(38%)	52
0:								
Basal period	4	0	—		2	0	—	
Preterminal period	0	4	—		0	9	—	
1-20:								
Basal period	4	6	9		6	5	9	
Preterminal period	4	10	9		4	3	9	
21-40:								
Basal period	5	12	6		4	9	7	
Preterminal period	4	8	6		4	5	7	
41-60:								
Basal period	1	4	2		1	2	4	
Preterminal period	5	0	2		4	1	4	
>60:								
Basal period	1	—	—		0	3	—	
Preterminal period	2	—	—		1	1	—	

TABLE 3. *Interval between Omission of Insulin and Terminal Admission.*

Interval	No. of Patients with Kimmelstiel–Wilson Lesions	No. of Patients without Kimmelstiel–Wilson Lesions
yr.		
<1	2	4
1-2	1	5
>2	2	1
Totals	5	10

of the former group and 6 of the latter needed no insulin for a year or more. Acidosis did not develop in any of these patients. Nine of the 15 patients had the clinical Kimmelstiel–Wilson syndrome; 4 of them were later proved to have the lesion, and 5 did not have it.

TABLE 4. *Changes in Insulin Requirement in Relation to Clinical Kimmelstiel–Wilson Syndrome.*

Insulin Requirement	Patients with Kimmelstiel–Wilson Lesions		Patients without Kimmelstiel–Wilson Lesions	
	Number	Average Change in Insulin Dosage	Number	Average Change in Insulin Dosage
		units		*units*
Increased	6	15	1	20
Decreased	15	18	6	22
Same	8	0	1	0
Totals	29	—	8	—

The clinical syndrome — that is, edema, albuminuria and hypertension — occurred approximately three and a half times more frequently in the group with the proved renal lesions than in the group without the lesions (Table 4). A decrease in insulin dosage was noted in the majority of patients (59 per cent) with this syndrome, regardless of the eventual pathological classification of the renal lesion. Nitrogen retention, edema and albuminuria analyzed as separate findings were also more common in the group with Kimmelstiel–Wilson lesions. The patients with nitrogen retention and edema were for the most part included in the group presenting the clinical syndrome and therefore reflected changes in the insulin dosage of that group. However, albuminuria was a common finding in patients both with and without Kimmelstiel–Wilson lesions, and less than half had a decrease in insulin dosage.

Classification according to the severity of the Kimmelstiel–Wilson lesions disclosed that the patients with increases and decreases in insulin requirement were nearly equally distributed between those with + or ++ and those with +++ or ++++ lesions (Table 5). The average decrease in insulin dosage was greater in the group with +++ or ++++ lesions, but the clinical Kimmelstiel–Wilson syndrome was also more prevalent in this group.

Twenty-five episodes of diabetic acidosis occurred in 14 patients with, and 11 episodes in 9 patients without Kimmelstiel–Wilson lesions (Table 6). The pathological classification of the lesions in patients who had diabetic acidosis associated with their terminal admission was as follows: +, 1 case; ++, 3 cases; +++, 2 cases; and ++++, 2 cases.

Discussion

Although amelioration in the severity of the abnormal carbohydrate metabolism of diabetes mellitus as evidenced by lower insulin requirement occurred in cases with proved Kimmelstiel–Wilson lesions, increases in insulin requirement also occurred. The net result was an over-all decrease of only 2 units in mean daily requirement. It was further noted that similar events took place in patients without the lesions. This was in contrast to the study of Zubrod et al.,[6] who found a decrease in insulin requirement amounting to 9 units in the patients with Kimmelstiel–Wilson lesions, and an increase of 33 units in the group without the lesions.

TABLE 5. *Changes in Insulin Requirement in Relation to Renal Disease.*

Insulin Requirement	Patients with + or ++ Kimmelstiel–Wilson Lesions		Patients with +++ or ++++ Kimmelstiel–Wilson Lesions		Patients with Other Renal Lesions		Patients with No Renal Lesions	
	Number	Average Change in Insulin Dosage	Number	Average Change in Insulin Dosage	Number	Average Change in Insulin Dosage	Number	Average Change in Insulin Dosage
		units		*units*		*units*		*units*
Increased	8	15	7	13	9	17	4	21
Decreased	10	14	12	20	14	21	5	18
Same	4	0	13	0	18	0	2	0
Totals	22	—	32	—	41	—	11	—

In patients of both groups who had the clinical syndrome of Kimmelstiel and Wilson (edema, albuminuria and hypertension), insulin requirement fell in most cases. This syndrome was more common in the patients with the Kimmelstiel–Wilson lesions of the kidney. Wilson, Root and Marble[8] previously noted a decrease in insulin requirement with the onset and progression of renal insufficiency, cardiac decompensation and blindness. The patients in the present

TABLE 6. *Occurrence of Diabetic Acidosis.*

Time of Occurrence of Acidosis	Patients with Kimmelstiel–Wilson Lesions		Patients without Kimmelstiel–Wilson Lesions	
	No. of Patients	No. of Episodes	No. of Patients	No. of Episodes
Before preterminal period	10	13	3	3
In preterminal period	3	4	4	4
In terminal period	8	8	4	4
Totals	14(26%)	25	9(17%)	11

study with the clinical syndrome of Kimmelstiel and Wilson demonstrated similar difficulties. In 5 patients followed clinically, detailed dietary histories indicated that a marked decrease in food intake may accompany the onset and progression of the syndrome. It is well established that dietary restriction promotes increased carbohydrate tolerance. Zubrod et al.[6] concluded that amelioration in the diabetes could not be explained on the basis of weight loss. Since edema, evident clinically, was present in 59 per cent of the group with Kimmelstiel–Wilson renal lesions and 21 per cent of those without the lesions, loss of body fat and lean mass could have taken place without changes in total body weight. Therefore, significant and prolonged decrease in food intake would not necessarily be reflected in loss of weight in these patients in the presence of edema. Decreased food intake may be an important factor in many of the patients with otherwise unexplained amelioration of the diabetes, and would not be evident from clinical records as they are ordinarily kept.

Pathologically, there was no striking correlation between the extent of the Kimmelstiel–Wilson renal lesions and either decreases or increases in insulin requirement. If the renal lesions per se had been causally related to the amelioration of the diabetes, it would be expected that decreases in insulin dosage would have occurred more commonly with the more advanced renal lesion. However, this was not observed.

Diabetic acidosis did not prove to be a rare event in patients with renal lesions of Kimmelstiel and Wilson. It occurred at least as frequently in patients with as in those without the lesions. Nor did the episodes of acidosis occur only before the development of the renal lesions, for 4 patients with + + + and + + + + renal changes had diabetic acidosis as a terminal event. With 1 exception, diabetic acidosis did not occur in patients with the clinical syndrome of Kimmelstiel and Wilson. This exception was in a patient who had had repeated episodes of diabetic acidosis during fourteen years of diabetes. These observations support the previous statement that the renal lesions per se are not necessarily associated with amelioration of the diabetes. The infrequent occurrence of diabetic acidosis in patients with the clinical syndrome further suggests that the syndrome may have an ameliorating effect upon the diabetes, possibly as a result of a decreased food intake.

Summary and Conclusions

The clinical records of 375 autopsied cases with diabetes mellitus were reviewed to explore further the circumstances leading to changes in insulin dosages during the course of this disease. Two selected groups of patients were compared, 54 with and 52 without Kimmelstiel–Wilson renal lesions.

Both amelioration and increased severity of the diabetes as judged by changes in insulin dosage occurred in patients without relation to their renal lesions. The over-all result of these changes in insulin dosage was a decrease of 2 units from the basal to the preterminal periods in both groups of patients. It is concluded that the alterations in insulin requirements are not causally related to the renal lesion.

Evidence is presented that amelioration of the diabetes is often, but not invariably, associated with the *clinical syndrome* of Kimmelstiel and Wilson, — that is, edema, albuminuria and hypertension, — which occurs in patients both with and without the proved renal lesions. In patients in whom this syndrome is present decreased intake of food may contribute greatly to an amelioration of the diabetes. Diabetic acidosis is not unusual, even in patients with advanced Kimmelstiel–Wilson renal lesions, but is uncommon in patients with the clinical syndrome of Kimmelstiel and Wilson.

There is no evidence in this study to support the thesis of Zubrod, Eversole and Dana that a specific type of diabetes, characterized by amelioration of the severity of the disease and infrequent occurrence of acidosis, is associated with the Kimmelstiel–Wilson renal lesions per se.

References

1. Kimmelstiel, P., and Wilson, C. Intercapillary lesions in glomeruli of kidney. *Am. J. Path.* **12**:83-98, 1936.
2. Kimmelstiel, P., and Porter, W. S. Intercapillary glomerulosclerosis. *New Eng. J. Med.* **238**:876-879 and 908-912, 1948.
3. Rifkin, H., Parker, J. G., Polin, E. B., Berkman, J. I, and Spiro, D. Diabetic glomerulosclerosis: clinical and pathologic observations with special reference to doubly refractile fatty cells and casts in urine. *Medicine* **27**:429-457, 1948.
4. Rich, A. R., Berthrong, M., and Bennett, I. L., Jr. Effect of cortisone upon experimental cardiovascular and renal lesions produced by anaphylactic hypersensitivity. *Bull. Johns Hopkins Hosp.* **87**:549-567, 1950.
5. Friedenwald, J. S. Diabetic retinopathy. *Diabetes* **2**:237-240, 1953.
6. Zubrod, C. G., Eversole, S. L., and Dana, G. W. Amelioration of diabetes and striking rarity of acidosis in patients with Kimmelstiel–Wilson lesions. *New Eng. J. Med.* **245**:518-525, 1951.
7. Robbins, S. L., Rogers, J., and Wollenman, O. J., Jr. Intercapillary glomerulosclerosis: clinical and pathologic study. III. Pathologic study of 100 cases. *Am. J. Med.* **12**:700-705, 1952.
8. Wilson, J. E., Root, H. F., and Marble, A. Diabetic nephropathy: clinical syndrome. *New Eng. J. Med.* **245**:513-517, 1951.

MEDICAL PROGRESS

MEDICAL EDUCATION IN RELATION TO RURAL HEALTH

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WHETHER medical schools accept, or have thrust upon them, outside responsibilities extending beyond the mere provision of four years of undergraduate training, they can by no means control the type of medical practice later to be undertaken by their graduates. The phrase *medical education*, as used in this title, therefore should not confine itself to activities under the domination of medical schools. Nor can the *rural health* of the present title refer alone to something that is dependent on the availability of medical services in the sparsely settled regions; rural health is not essentially different from other kinds, and health has economic and biologic components as well as geographic; however defined it is a state that must respond to its total climate or environment rather than a single increment thereof. Medical education and rural health are starting points, but to simplify the relation as one of supply and demand for a somewhat inelastic product would be to create a narrow approach. The responsibilities involved are community wide.

Comment and correspondence in this journal have indicated deep concern in the minds of many people regarding the quality of medical education now provided for those who want, or might want, to enter the general practice of medicine.[1-3] By means of questionnaires the Massachusetts Academy of General Practice has surveyed medical students and general practitioners (but apparently not medical faculties) for grass-roots opinion. Although it confined itself to Massachusetts doctors and schools, a good response was obtained. The president of the Academy commented as follows on the result:

> . . . [the profession] must take positive steps within the medical schools and hospitals to provide communities with more and better general practitioners. We can conclude from the survey that unless constructive conservation measures are taken immediately, the general practitioner — the family doctor so essential to the treatment of the whole patient — may become obsolete.

Such professional anxiety is not new. Thirty years ago an ex-president of the Massachusetts Medical Society said:

> Our ranks are fast thinning; recruits are few and far between. In fact the family doctor is already a rare bird, hardly ever to be found nowadays except in remote rural regions beyond the reach of the specialist's limousines. The reasons for his disappearance are plain enough. . . It is only the natural result of modern medical education. What other product than specialists can be expected of a medical school where all the clinical instruction is given by specialists?

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As a result, in part, of the meeting at which these words were said it was decided that something might be done about it, and an attempt was made. A series of lectures under the general subject "Physician and Patient" was inaugurated at Harvard Medical School, some of the participants coming from Baltimore, Chicago and elsewhere. Many of the lectures were printed, and some became classic additions to the medical literature. Such a one was "The Care of the Patient" by Francis W. Peabody, but as Dr. Peabody later wrote, "So little can be done by talking — after all the only real thing is close daily contact with the highest type of physician." Since in medical education didactic instruction comes under the category of "talking," it may be hoped that Dr. Peabody would be pleased with the progressive reduction in didactic teaching that has taken place in medical education over the past two decades. A more serious problem for medical schools may be a limited supply of the "highest type of physician." How are such physicians recognized, and what are the criteria by which medical schools select their faculty members? If these questions were answered for the medical schools across the country one would find such widely diverging viewpoints and practices that the formulation of a statement applicable and agreeable to all would be impossible.

SCHOLARSHIPS FOR RURAL HEALTH

A more direct exploration of the relation between medical education and rural health followed the establishment by the Commonwealth Fund, in 1930, of a series of scholarships in three schools, for students who would agree to locate in rural areas for a period of at least three years after completion of medical school and internship training. The three schools were located in Boston, Nashville and New Orleans, and the arrangements made were generous from the student's point of view. He was given $1,200 for each of the four years and after internship was generally assisted in equipping his office. The intended purpose was to remove all financial obstacles from the path of the student who professed to be interested in rural practice. Among more than 50 students selected at one of the three schools there were a few scholastic failures, and one or two chose to release themselves by repayment of funds; but the great majority met the terms of the agreement and did practice for at least three years in a rural community. In steering these students it was found that the type of internship called for was sometimes difficult to arrange and needed some con-

trol. It was then believed that both obstetrics and pediatrics were important parts of rural practice, an assumption no longer universally held. Whatever the content of the internship selected, the hospital's example of medicine as it is being practiced is more impressive to the young physician than that of the medical school.

Wartime interruptions now make it difficult to assess the long-time effectiveness of this first attempt to underwrite the medical education of those hopeful rural practitioners. Perhaps half of them returned to general practice in more or less rural locations. Some were conspicuously successful, returning to the originally selected locations and being welcomed back as community leaders. For more of them a new location seemed to have greater appeal. It is apparent that the successful rural doctor must have appropriate character and personality and have married the right girl, as well as selected the right spot for practice. With these unpredictable hazards, different degrees of success in attaining the final goal are to be expected. It is the old old riddle: how do you pick a winner?

Although the Commonwealth Fund never presumed to answer this question it did, in the 1930's, pioneer a method that has since been adopted with various modifications in other places. A few later examples of underwriting the education of a student who will obligate himself to repay in rural service may be cited.

State of Alabama County Scholarships are issued to students who are in financial need, are residents of a county in the State and are registered in the Medical College of Alabama. Of course, most of the counties of Alabama are essentially rural; a scholarship may be granted to 1 resident in each county, the maximum amount being $1,600 over the four-year period. Mandatory repayment is in the form of practice in the county of which the applicant is a resident for a period that is variable but is not to exceed five years.

The Illinois Agricultural Association, in co-operation with the Illinois State Medical Society, maintains a student loan fund for residents of counties in Illinois where physicians are needed. The maximum loan for a year is $1,000, and the maximum total loan is $5,000. The recipients must practice general medicine in communities of less than 5000 population in their home counties until the loan is repaid in full. This program has been in operation since 1947, and there are now about 60 participating students and doctors. Most of the doctors are still in service.

The Iowa State Medical Society Educational Fund is available for loans to Iowa residents, both medical students and interns, the total maximum amount being $6,000. The recipients must practice medicine in a rural community in Iowa for at least three years. Repayment of the loan is mandatory, beginning with the third year in practice. About 20 students are now participating.

The Kentucky State Medical Association sponsors a loan fund from which $800 a year is available to medical students, preferably at the University of Louisville, who will agree to practice for as many years as financial aid was extended in communities of less than 10,000 population, which must be selected on the basis of medical need. Repayment is mandatory, with interest, after a year of practice. About 70 students and graduates are now participating, and about 20 are now in active practice. At least 6 have completely fulfilled their financial and moral obligations. This fund has been in operation since 1946.

The Michigan Foundation for Medical and Health Education, Incorporated, offers loan funds to residents, interns and senior medical students in Michigan's two medical schools who will agree to practice in a community of less than 5000 population for a minimum of three years. Repayment is required, beginning a year after the graduate enters practice. The Foundation is supported by contributions from Michigan doctors.

The Minnesota State Medical Association has established a fund that provides outright grants of $1,000 a year for four years to medical students who will agree to practice in a community of 5000 population or less in Minnesota for a period of five years. The program is restricted to the University of Minnesota Medical School.

The Mississippi State Medical Education Board administers a scholarship plan that has already placed a great many doctors in active rural practice. The student agrees to practice a minimum of two years in a rural area; repayment is by service, each year of practice in the designated area reducing the loan by a fifth. Since this program was initiated, no white or Negro medical student who was qualified to enter a Class A medical school has been denied that opportunity for lack of money. In the future Mississippi can expect an annual supply of 50 physicians through this program, and since the attrition by death for the past six years has averaged about 40, the scholarships alone will more than offset the loss. The funds are appropriated by the legislature biennially.

The Ohio State Medical Association provides a scholarship for Ohio rural residents of $500 per year, in return for which rural practice is "encouraged." No repayments are required. At the time of writing there were only 5 participants.

Scholarships and loans are provided in other states without restriction regarding size of communities that may be selected for practice. In some of these, as in South Dakota, practice anywhere within the state is a contribution to rural health. Scholarships and loans represent a primary flow of interest and advantage toward individual students who have been hopefully selected as recruits for rural service; they are best described as a recruiting device. They do not in any way influence the quality of medical education, and it should be emphasized that they may well add to the administrative burdens of medical educators without

in any way altering or improving the instruction given.

This discrepancy has already been recognized and acted on. At the University of Colorado, for example, an estimate is made of the over-all cost per student for operating the Medical School. (In any modern school in this country such an estimate will be considerably in excess of the stated tuition fee.) With the cost determined medical education is then offered to residents of surrounding states at this over-all figure. A neighboring state is thus able to appropriate funds for the medical education of its residents, in Colorado, without undertaking the expensive and frequently impossible task of operating another medical school in a rural area. A group of states in the southeast corner of the nation have organized a regional education plan under which a student in one state may be sent to the schools in participating states for any specialized instruction not available in the home state. With this plan the schools giving the instruction are also remunerated for their over-all teaching costs by the student's home state. A similar plan for the New England states has already been broached, and could well be developed to serve both medical education and rural health in this area.

The fundamental supposition of all devices that make medical education available to rural residents is that the country boys and girls will naturally wish to return to the country to practice, and will do so with less urging than the city students, already contaminated with the scholarship habit before they know what they want to be educated for.

Medical Curriculums for Rural Health

In the 1930's changes began to appear in medical curriculums, somewhat timidly at first, but tending more and more to develop opportunities that might bring the medical student in personal touch with the sick person, with the family, with the home environment, with the social background and with the family doctor. There gradually developed, as there often does, a vocabulary to indicate a changing point of view or emphasis. Talk began about *the whole man, comprehensive medicine, mosaic medicine, holistic medicine, correlation* and *integration.* One was reminded of the collegiate definition of the well rounded man as the one who had tasted all 28 flavors!

It is hard to know just how and where the return of the preceptor began, but by 1930 he had reappeared, and by 1935 the faculty of one school listed as many as 30 preceptors in its annual bulletin. Although he was at first frowned upon by the official American Medical Association, the preceptor gradually became respectable again, and since the end of the war preceptors have made not only a colorful addition to medical education but also what may become a substantial contribution to rural health. For the first time since the affectation of the long white coat the general practitioner is, in some regions, in a position to compete on equal terms for the interest and guidance of undergraduate medical students. His foot is in the door; a few examples follow.

The University of Wisconsin has a well known program of preceptorship in which the fourth-year student is given experience designed to acquaint him with the conditions of both rural and urban practice. He spends twelve weeks with a general practitioner, working with him on home visits and in office and hospital practice. At the University of Nebraska College of Medicine a twelve-week period of preceptorship has recently been added to the curriculum and is a requirement for graduation.

The University of Tennessee conducts a family general-practice clinic within the outpatient department. Since this school serves an area that particularly needs general practitioners, the primary purpose is to interest the students in this type of practice. There are no specialists on the staff of the clinic, but patients may be referred to specialists elsewhere in the department. Students are assigned for the last five months of their training. In connection with this clinic a family-care program is in operation. In this program each student acts as family physician for a single family for the period of a year. During this year he calls on the staff of the general-practice clinic for any help or consultations.

Students at the University of Pennsylvania have what is perhaps the most highly developed of any of the family-care programs. They act as health advisers to particular families at home and in the hospital for the four years of their medical training. The emphasis is said to be on a gradual increase in student responsibility with the problems that are encountered from month to month and from year to year, in contrast to the more concentrated experiences of other domiciliary care programs. It is obvious that none of the domiciliary or family programs can be both continuous and total; they must each be operated within a fraction of the student's time. Their quality may be roughly measured by the ratio of instructing and supervising time to the time of actual assignments.

Since 1950 a program has been developed at the University of Kansas School of Medicine that provides a large role for the general practitioner.[4] There, the preceptors are selected from towns of 2500 population or less and must be solo practitioners. They provide board and room for the student, who spends five or six weeks with them, often living in the home, eating with the doctor, making every house call and getting up for every emergency with him. This program is complemented by circuit courses and postgraduate instruction for the practicing physicians of the State at the School in Kansas City. In 1953-1954, 79 per cent of the outlying preceptors enrolled in courses at the University of Kansas, and of the total enrollment in the postgraduate courses 991 were Kansas physicians (total physicians in State, 2100). Whereas the State of Kansas consistently lost more physicians than it gained in the years 1900 to 1950, in

both 1950 and 1951 it gained 100 physicians. In Kansas towns of 1000 population or less 220 additional general practitioners have now begun to practice. Looking toward the future, this medical school contemplates the establishment of general-practice residencies and a broader staffing of its postgraduate division. Surely, all these things will raise the level of rural health in the region of the Sunflower State, and must already have raised the local reputation of the medical profession.

Reorganization of the outpatient department at the University of Oklahoma Hospitals in 1952 provided a new opportunity for students to orient themselves toward medical practice. Most of the medical specialty clinics were eliminated, and the specialists were assigned to the medical clinic. The few specialty clinics that were retained were conducted without students, who were assigned to the clinic for general medicine for twenty-six weeks of their fourth year. The altered attitude toward the specialties, as well as the fact that referring a patient meant referring him to one's self in another clinic, reduced referral of patients in the department approximately 70 per cent. Both the traditional competition for "cases" and the tendency to shift onerous responsibilities to other clinics were lessened.[5]

The method of creating a new division or department of general practice, as at Tennessee, and that of consolidating and eliminating previously existing departments, as at Oklahoma, although they seem to point in opposite administrative directions, are serving the same purpose, that of emphasizing general practice. They indicate a need and a desire to make medical education more representative of medical practice. The medical curriculums of the nation are not rigid, nor is the thinking of medical educators. The curriculum at Western Reserve is being radically made over from stem to stern (which may or may not be of significance to rural health). There can be no best pattern for all to follow, for each school must scan its own resources and other commitments before making major alterations in its curriculum. If the final criteria can be not how much taught but how much learned, these experiments will all be worth while.

Physician Distribution for Rural Health

There has been much recent progress in creating understanding on the part of rural populations concerning availability of medical services and what improvement can reasonably be expected. Immediately after the war there were inflammatory pronouncements about doctor shortages that, fanned by political motives, threatened in many places to bring about an unwise and hasty multiplication of medical schools. There were at first no factual reservoirs from which these fires might be quenched, but now there is at hand the needed information and to a considerable extent the medical organization with which to proceed toward continuing improvement in rural health, wherever the rural dwellers themselves are sufficiently interested to participate.

After a seven-year study, the Bureau of Medical Economic Research of the American Medical Association has divided the United States into 757 "trading areas," disregarding such unrealistic barriers as city, county and state boundaries. It is within these trading areas that people naturally find their supplies and services, and each of these areas had at least one physician in active private practice. Today, transportation and communications make it unnecessary for a physician to be located in every hamlet, village or town. A patient who is 25 miles away from his doctor today is actually closer in terms of time than he would have been if he was only 3 miles away fifty years ago. When a map is prepared showing the sections of the United States that are outside a 25-mile radius from the closest town with a physician in active practice, it is found to include only a sixth of the land area of the United States. Much of this area is wasteland, salt flats, Indian Reservations, cattle ranches and, for the most part, uninhabited.[6]

This is not to assume that the distribution of physicians in the United States has been perfected, nor that it will reach a static form at any future time. Much of what has been accomplished has been due to, and more may yet be expected from, the work of the Council on Rural Health of the American Medical Association. This council was formed in 1951 as the outcome of activities begun several years earlier in which the American Farm Bureau Federation, the Milk Producers Federation, the Grange and the Extension Services of the Land Grant Colleges co-operated with a committee on rural health of the Association to give leadership to communities that might be interested in their own health problems and to encourage farm persons generally to help themselves obtain and hold a physician, to build medical facilities or a hospital and to acquire modern diagnostic and therapeutic equipment, and to teach them how a community can educate its residents to use properly the physician and medical facilities that it acquires. Many of the state medical associations and societies now have corresponding rural-health committees. Ten national conferences on rural health have already been held, most of which have been addressed by the presidents and other high officials of the American Medical Association.

During the summers of 1952 and 1953 the Council on Medical Service of the Association employed medical students to study the physician-placement programs in a number of the states. A series of reports have now been published describing placement activities in Ohio, Virginia, Nebraska, Indiana, Missouri, Illinois, Texas and Mississippi.[7-10] In all these states there are in operation placement services that undertake to keep and match lists of communities needing physicians and of physicians wanting information about locations. (It is generally agreed

that the most plaintive requests and glowing descriptions come from people who are anxious to rent or sell a piece of real estate.) Many of these services grew out of wartime procurement and assignment activities, and they continue to provide a useful clearinghouse function. Frequently, the activities in these states have branched out on a local level into the type of educational work referred to in the last paragraph as being pioneered by the Council on Rural Health.

Mississippi is the only state where three separate organizations — the state Board of Health, the Medical Education Board and the Mississippi State Medical Association — have been prompted to assist communities in need of physicians and physicians seeking suitable locations in which to practice. Because it is primarily a rural state the over-all benefits that have already accrued are great. (It was not long ago that Mississippi was considered a dismal swamp by most public-health orators.) The number of physicians has increased from 1112 in 1946 to more than 1500 at the present time. On account of the scholarship plan already referred to, many and probably most of these new physicians have been located in rural areas. According to the executive secretary of the Mississippi State Medical Association, the number of communities at present without a physician is statistically insignificant.

Community Action for Rural Health

Community resources for rural health are seldom natural resources; they are the product of community interest, effort, spirit and determination to obtain whatever can be reasonably supported and can be expected to serve and promote the health of the citizens. Rural health is community health; it needs community facilities and understanding. This means not only medical services but also clinical or hospital facilities, public-health or school-health programs perhaps, nursing services or whatever else the community may want after it has discussed its needs and gauged its capacity to acquire them. Interested individuals in any community can easily obtain the information they need, get expert advice or visit similar communities where the same problems have already been solved. The continuing success and growth of the annual conferences on rural health demonstrate the growing momentum with which this movement now rolls on. Substantial aid can frequently be obtained by public grants or from philanthropic private sources, but these are all secondary to community initiative, which is the vital force that must be harnessed. The standard public-health device for translating interest into action in health matters is the organization of what have become known as community councils, which is the name given to a group of citizens who will meet, discuss and develop public-health activities in their own home towns. At the local community level they constitute the very best device to promote rural health.

On the other hand the community council is not the only method of prompting public action. Some fairly large rural areas have been organized on a regional basis. In the matter of hospital construction, for example, one can again refer to the erstwhile modest state of Mississippi. There, a commission was quick to act on the Hospital Survey and Construction Act of the Seventy-Ninth Congress and developed an aggressive program to meet its hospital needs.[10] This has already achieved more than half its original objective. Fifty hospitals have been completed or are approved for construction. Many of them are small, 25 to 50 beds, but they will bring the needed facilities "within about 20 miles of every home in the state." The county health-department program has likewise added to the medical resources of Mississippi in the rural districts. In towns where suitable office space was not available it has been provided in the new health centers. These offices where local physicians carry on their practice are well equipped and apparently have been a favorable factor in getting young doctors into the communities that have the greatest need for their services.

The development of systems of regional medicine under private auspices, such as that of the Bingham Associates, in Maine and elsewhere is well known. To what extent private funds may compete with public monies in the future development of these arrangements is uncertain. In general, private funds tend to confine themselves to limited areas or try to show someone else how it can be done, whereas public funds tend to duplicate excessively until a given political pattern has been completed. The masses of rural dwellers in this nation will undoubtedly prefer to work out their own salvation in matters of health.

It was pointed out above that the medical curriculum and medical education in this nation are not static. It may be said in closing that neither is rural health. Many an industrial worker now lives in the country, with well and cistern, whereas the farmers themselves may enjoy a cosy suburban subdivision. Just as the doctor can get out to the country so the countryman can get in to the larger centers of population. Rural health will continue to be where one finds it, but one will only find it where it has been wanted, nurtured and supported by a group of people who appreciate it and are willing to sustain it.

References

1. Editorial. Vanishing American? *New Eng. J. Med.* **251**:283, 1954.
2. Editorial. "Local medical doctor." *New Eng. J. Med.* **251**:754, 1954.
3. Funk, J. W. Regarding "vanishing American." *New Eng. J. Med.* **251**:757, 1954.
4. Dimond, E. G. General practitioner and medical school. *J.A.M.A.* **156**:95-97, 1954.
5. Colmore, J. P., and Wolf, S. New design for service and teaching in outpatient department. *J.A.M.A.* **156**:830-833, 1954.
6. How far from physician? *J.A.M.A.* **152**:718, 1953.
7. Council on Medical Service. Placement of physicians by Ohio State Medical Association. *J.A.M.A.* **151**:665, 1953.
8. *Idem.* Placement of physicians in Illinois. *J.A.M.A.* **153**:671-674, 1953.
9. *Idem.* Placement of physicians in Texas. *J.A.M.A.* **153**:1473-1476, 1953.
10. *Idem.* Placement of physicians in Mississippi. *J.A.M.A.* **154**:1119-1121, 1954.

MEDICAL INTELLIGENCE

TRICHINOSIS WITH MYOCARDITIS*

Report of a Case Treated with ACTH

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THE mortality in trichinosis, as listed by Gould,[1] is about 5 or 6 per cent. The chief danger and most frequent complication is myocarditis, most deaths resulting from the development of congestive heart failure and bronchopneumonia.[1]

The use of ACTH and cortisone in the treatment of trichinosis, as first described independently by Davis and Most,[2] by Rothenberg[3] and by Luongo et al.,[4] offers hope that the acute phase of the disease may be modified and the mortality lowered. To date, 6 cases of trichinosis treated with ACTH and 3 cases treated with cortisone have been reported in the American medical literature.[2-7] In all cases clinical improvement was noted. In 3, myocarditis was present.[5-7]

In the following additional case of trichinosis complicated by myocarditis ACTH therapy resulted in prompt and lasting clinical recovery from the myocarditis.

CASE REPORT

A 40-year-old man was admitted to the hospital on July 28, 1954, with the chief complaints of severe generalized muscle pain, headache and fever of 5 days' duration. During the period before admission the temperature had risen to 106°F. Two weeks previously he had experienced diarrhea, nausea and vomiting for 2 or 3 days. One week after these gastrointestinal symptoms had subsided, his wife noted puffiness about his eyes. He stated that 5 days before the onset of the diarrhea he had purchased and eaten uninspected pork from a wholesale meat market; this meat had not been shared with other members of his family.

Physical examination revealed an acutely ill, well nourished man. Slight periorbital edema was present. There was marked nuchal rigidity, with muscle spasm involving the arms, abdomen, back and legs. Dorsiflexion of the feet caused severe calf pain, as in the Homans sign. The thigh, arm and back muscles were extremely tender to palpation. The remainder of the physical examination was negative. The heart tones were of good quality, with a normal sinus rhythm and rate.

The temperature was 103°F., the pulse 88, and the respirations 20. The blood pressure was 110/70.

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Examination of the blood showed a white-cell count of 13,050, with 41 per cent eosinophils. The red-cell count, hemoglobin, urine, spinal fluid, an x-ray film of the chest and an electrocardiogram (Fig. 1) were all reported as normal.

A skin test for trichinella performed the next morning was positive within 15 minutes.

With salicylates and analgesics the spiking fever gradually subsided so that by August 8 the patient had become afebrile. However, muscle pain and tenderness was still quite severe, and there was evidence of severe muscle weakness and wasting. On August 9 the white-cell count was 14,800, with 26 per cent eosinophils. A 2d electrocardiogram showed occasional ventricular premature beats, inverted T wave in Lead V_1 and diphasic T waves in Leads

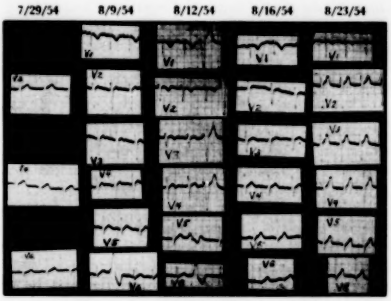

FIGURE 1. *Serial Electrocardiograms, Showing Development Followed by Resolution of Myocarditis (Only V Leads Are Shown).*

July 29. Routine tracing with standard leads, unipolar limb leads and Leads V_1, V_2 and V_6, interpreted as normal, was taken early in the illness.

August 9. Leads V_1 and V_2, showing occasional ventricular premature beats, inverted T wave in Lead V_1, and diphasic T waves in V_2 and V_3.

August 12. Premature beats are much more frequent with inverted T waves in Leads V_1, V_2 and V_3 and diphasic T wave in Lead V_6. This was interpreted as a myocarditis.

August 16 and 23. T-wave changes show return to normal. The inversion of the T wave in Lead V_1 is apparently a normal variant in this patient.

V_2 and V_3 (Fig. 1). The pulse was 100. At this time no clinical findings of myocarditis were detected besides occasional premature beats and the slight tachycardia with a normal temperature. There were no signs of congestive heart failure.

On the following day the pulse had risen to 112, with more numerous premature beats, and on August 11 a gallop rhythm was detected. These changes were interpreted as indicating serious myocarditis, with impending congestive heart failure. ACTHAR Gel was begun that afternoon in a dosage of 40 units intramuscularly every 12 hours. The patient was placed on a low-salt diet with supplementary potassium chloride, 1 gm. 4 times a day. The next morning the white-cell count was 13,900, with a remarkable decrease in the number of eosinophils — to 2 per cent. An electrocardiogram on this day showed more fully developed changes suggesting myocarditis, with T-wave inversion in precordial Leads V_1 to V_5 and a diphasic T wave in Lead V_6 (Fig. 1).

Response to steroid therapy was quite prompt, with considerable improvement in the muscular pain and tenderness within 24 hours. Of greater significance was the fact that by August 14 the pulse rate had dropped to 78, no premature beats were heard, and the gallop rhythm had disappeared.

The dosage of ACTHAR Gel was gradually reduced over the next 10 days, and the drug was discontinued on August

23. Electrocardiograms taken on August 16 and 23 showed reversal of previous changes and a return to normal (Fig. 1).

With clinical recovery from the myocarditis physiotherapy to strengthen the less painful but now soft, flabby muscles was instituted. He had lost 18 kg. in weight and was profoundly weakened. Testosterone propionate, 25 mg. intramuscularly every other day, was given in an attempt to restore positive nitrogen balance and prevent more muscle wasting.

The patient slowly recovered strength. Diarrhea appeared in the 3d week of illness and persisted despite the usual measures for an additional 6 weeks and then cleared. He was discharged on August 29, and was readmitted for further study 2 weeks later because of the diarrhea. Stool examinations and complete gastrointestinal roentgenograms, including small-bowel studies, failed to reveal any cause for the diarrhea. During the 2d admission a gastrocnemius-muscle biopsy showed numerous encysted trichinella larvae (Fig. 2). The eosinophilia had recurred, but fever had not. After 4 weeks the eosinophilia and the diarrhea cleared spontaneously.

Discussion

In trichinosis myocarditis may appear as early as the second week of the disease. The trichinella larvae invade the myocardium but never encyst, setting up, however, an inflammatory response within the myocardium. Most of the trichinella are destroyed, and the remainder re-enter the blood stream or escape into the pericardium. In fatal cases of myocarditis, death usually occurs between the fourth and the eighth week.[1]

Since the acute inflammation attendant on the migration of the larvae into the myocardium constitutes the main threat to life, any agent that will suppress this inflammatory response should enable the physician to tide the patient over the period of greatest danger, even though the trichinella larvae are unaffected. Though the possibility is disputed by some, recovery from the myocarditis of trichinosis is currently believed to result in cure without residual cardiac damage.[1]

Davis and Most[2] have shown by serial muscle biopsies that ACTH does alter the inflammatory response in skeletal muscle. Myositis was much less pronounced during therapy and again became prominent after withdrawal of the steroid.[2]

We believe that a similar suppression of inflammation occurs in the myocardium under the influence of ACTH, as demonstrated by the clinical response and serial electrocardiograms in the case reported above. Before administration of ACTH tachycardia with a gallop rhythm was increasing, and ventricular premature beats were becoming very frequent. Within thirty-six hours of the administration of ACTH the cardiac rate and rhythm became normal, and the inverted T waves seen in the precordial Leads V_2 to V_4 of the electrocardiogram again became upright.

Figure 2. *Photomicrograph of the Gastrocnemius Muscle, Showing Early Encystment of Three Trichinella Larvae, with Intense Lymphocytic Infiltration of the Surrounding Tissue (X30).*

The reappearance of diarrhea prolonged the disease but did not produce any real danger. Of great importance is the fact that a rapidly advancing and potentially dangerous myocarditis appears to have been quickly aborted.

Summary

A case of severe trichinosis with myocarditis is presented. ACTH therapy produced clinical improvement and prompt suppression of the myocarditis.

References

1. Gould, S. E. *Trichinosis*. 356 pp. Springfield, Illinois: Thomas, 1945.
2. Davis, W. M., and Most, H. Trichinosis: case report with observation of effect of adrenocorticotropic hormone. *Am. J. Med.* **11**:639-644, 1951.
3. Rothenberg, F. Treatment of trichinosis with cortisone. *J. M. Soc. New Jersey* **48**:517, 1951.
4. Luongo, M. A., Reid, D. H., and Weiss, W. W. Effect of ACTH in trichinosis: clinical and experimental study. *New Eng. J. Med.* **245**:757-760, 1951.
5. Solomon, C., and Seligman, B. Response of trichiniasis to adrenocorticotropic hormone (ACTH) therapy. *New York State J. Med.* **52**:1444-1446, 1952.
6. Roehm, D. C. Trichinosis: report of case manifesting myocarditis, encephalitis and radial neuritis: response to ACTH: review of literature regarding erythrocyte sedimentation rate. *Ann. Int. Med.* **40**:1026-1040, 1954.
7. Rosen, E. Cortisone treatment of trichinosis. *Am. J. M. Sc.* **223**: 16-19, 1952.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41101

PRESENTATION OF CASE

A twelve-year-old girl was admitted to the hospital because of pain and swelling in the right foot.

Two years previously she was said to have had a fracture of a small bone on the lateral aspect of the right foot. This condition cleared, and she remained well until a year later during the winter, when episodes of swelling, tenderness and pain occurred in the right heel when it bore weight. Associated with these episodes was a temperature ranging up to 100 or 101°F. She was well during the next summer, but the episodes recurred with increasing frequency a year before admission. Between episodes signs and symptoms were absent until six months before admission, when it was noted that the foot remained swollen with some tenderness. This failed to respond to two courses of cortisone therapy, one for five days and the other for ten days. For several months before admission there was an increase in pain, swelling and local heat over the right heel. The temperature ranged up to 101°F. Physical examination during this time showed swelling of the metatarsophalangeal joints as well as the subastragalar joints. The erythrocyte sedimentation rate was elevated. Blood and urine studies disclosed no abnormalities. In spite of bed rest and a bivalved cast the swelling increased. Aspirin produced some symptomatic relief. There was no history of disease of any other joints.

Examination of the heart and lungs showed no abnormalities. There was considerable fluctuant swelling of the right subastragalar region extending anteriorly along the plantar aspect of the foot. Erythema and increased local heat were also noted. Dorsiflexion and plantar flexion of the foot were full, with some discomfort at the extremities. Subastragalar motion was limited and somewhat painful. The remaining joints of the right foot and elsewhere in the body were unremarkable.

The temperature was 99.4°F., the pulse 100 and the respirations 20. The blood pressure was 110 systolic, 60 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 11.5 gm. per 100 cc., a white-cell count of 7700, with a normal differential, a sedimentation rate of 43 mm. per hour and a hematocrit of 35 per cent. The total protein was 7.6 gm., the calcium 8.9 mg., the phosphatase 5.1 units, and the uric acid 4.4 mg. per 100 cc. A tuberculin skin test in dilution of 1:100 was negative in forty-eight hours. X-ray films demonstrated a normal left foot. There was marked demineralization of the bones of the right lower leg, ankle and foot. The entire right os calcis showed widespread destruction, with preservation of the articular surfaces of this bone and of the contiguous bones. The other tarsal bones of the right foot were osteoporotic but not obviously destroyed. There was extensive soft-tissue swelling of the entire right foot and ankle (Fig. 1 and 2).

On the eleventh hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. MARTIN H. WITTENBORG*: At the start I should say that in viewing this case yesterday I got more information from the x-ray films than from the clinical material, and this lies in the nature of the pathologic process — not the examiner. Many radiologists interpret the history and physical findings in the light of what is seen in the x-ray films. The clinician may read an x-ray film with prior prejudice owing to his own findings in the history and physical examination. In the trade, that is known as reading too much into the films. I hope that I shall not do the same thing to the history.

I find very little in the history on which to come to any conclusion; I suspect that the attending physician, when he saw the patient early in the course, was in the same position. From the history it is apparent that I am dealing with an inflammatory response — in the most general sense of pain, swelling and heat — that was chronic and represented either a local process with a mild systemic reaction or a systemic disease with a local manifestation. On the physical examination there was definite swelling, which I gather was in the ankle joint. Painful motion was present both on flexion of the ankle and on subastragalar motion. I think that is quite significant. The absence of other physical signs and of other joint involvement with an increase in the sedimentation rate is exceedingly significant. I think by this time it is apparent that we are not dealing with a systemic disturbance with local manifestations, such as that seen in rheumatoid arthritis or rheumatic fever, in which we frequently see an inflammatory swelling of the synovia, but that we are dealing primarily with a local process, with some systemic reaction.

*Radiologist, Children's Medical Center.

In certain diseases, now well known to medicine, the clinical manifestations and physical findings are so nonspecific that the clinician can hardly suspect their presence but can readily recognize them from the x-ray examination; among such conditions are osteoid osteoma and some of the chronic low-grade osteomyelitides, which do not enter into the differential diagnosis here. I think the fact that the tuberculin test was done early and was negative is very important because tuberculous synovitis may give just this sort of story. It may escape detection until there has been major destruction of the bone or interference with the actual weight-bearing processes of the bone or joint or the development of a cold abscess that presents where the physician can actually see or feel it. In my experience, if the tuberculin test is negative in a

FIGURE 1. *Roentgenogram Taken Three Months before Admission Showing Early Destructive Changes in the Anterior Portion of the Calcaneus, with Coarsening and Some Irregularity of the Osseous Trabeculae in This Region. There is a soft-tissue mass (arrows) of the plantar aspect of the foot.*

child of this age, we can practically exclude tuberculosis even before looking at the x-ray films.

I might present the films we have. The first set of films, apparently taken elsewhere over two years before admission, was interpreted as showing a small fracture in the head of the fifth metatarsal. There is a small linear radiolucency there. I do not think it is relevant to the case because on subsequent films it is no longer present. The x-ray films taken twenty-two months before admission, when the patient was having intermittent episodes of pain on weight bearing, with a little swelling, are normal. There is no evidence of a local disturbance. At this stage I think the clinicians may have suspected that she had one of the collagen diseases, such as rheumatoid arthritis or rheumatic fever, with which most patients have pain and swelling actually in the joint and the film often shows an inflammatory type of swelling of the periarticular soft tissue. In my experience tenderness in these cases is best elicited by pressure on the medial and lateral aspects of the joint just at the level of the joint space, thus putting tension on the joint space. In the case under discussion the tenderness was in the foot and later was definitely localized in the heel, although on looking at the x-ray films I confess that I cannot be certain of the presence of any disease there at that time.

X-ray examination fourteen months before admission revealed distinct changes. In the right foot there is definite alteration of the bony trabecular architecture in the os calcis and soft-tissue swelling involving the region around the os calcis but not the type of swelling that is characteristic of synovitis or changes in the joint. When one interprets x-ray films of bones, one must pay a great deal of attention to the trabecular architecture and interpret any alterations in the light of bone physiology. In this case the previous films are normal ones, and yet in these films there has been a rearrangement of the trabecular architecture in this area that I think is highly significant. The trabecular pattern is usually deposited according to stress. Here, there is a considerable amount of new and very coarse trabeculation along the weight-bearing area. Normally, cancellous bone is composed of the little spicules with considerable overlap but forming a whole lacy network, with the trabecular pattern laid down according to the weight-bearing stress lines. In the case under discussion there has been rearrange-

FIGURE 2. *Progressive Destruction of the Calcaneus, Now Associated with a Huge Soft-Tissue Mass.*

ment of the stress lines that could have resulted if the cartilage in the knee had slipped and the weight was being thrown on another part of the foot or if there had been hip disease. In this particular case the clue lies in the fact that there is nothing abnormal elsewhere. The rearrangement is localized to a small amount of the weight-bearing area, with areas of absence of trabeculae and actual holes in the bone. At this stage I should interpret the findings as representing a definite abnormality, probably a local destructive lesion, and I should wonder about early osteomyelitis, early inflammatory destruction and neoplasm.

I cannot make an etiologic diagnosis at this stage because this is relatively early; however, I should like to say a word about the differential diagnosis. In the presence of chronic osteomyelitis, if there is a hole in the bone there is a reaction of the stroma to the destructive process. There is also inevitably evidence of healing. When destruction takes place there is a

local toxic effect but also attempts at healing with amorphous calcareous material along the margin; healing and destruction go on simultaneously in every case of chronic osteomyelitis, with the exception of those that are treated early with penicillin. The clinical data given make osteomyelitis seem unlikely. In a case like this the practical problem is important. The radiologist's responsibility does not stop with a description of the lesion: he must give an interpretation that is most useful in the handling of the medical problem. I should like to follow such a lesion to see whether a stromal reaction occurs within a very short time; if not, I should have to assume that there was a destructive process other than osteomyelitis.

On the next set of films, taken three months before admission, the picture is quite different (Fig. 1). Now there is considerable rearrangement of the trabecular pattern, with areas of loss of bone. The trabecular pattern is not laid down in stress lines but apparently actually around something that makes me very suspicious that there is a space-occupying lesion in the bone. There is a great deal of swelling. The picture is an exaggeration of that seen before. There is still no evidence of healing and no indication that the patient had received antibiotic agents. The final picture at the time of admission reveals quite a dramatic change (Fig. 2). In the lateral view of the right foot, in addition to the small focal areas of destruction with a rearrangement of some of the trabeculae around them, there are massive areas of destruction and swelling, which represent soft-tissue mass.

The foot is one of the most difficult areas in the body in which to evaluate inflammatory swelling because the engorgement of vessels in the soft tissue cannot be seen on account of the connective-tissue trabeculae in little cells of fat that simulate the same appearance. Here on the heel, where we ordinarily look for the picture of apophysitis, we see a sharp, clear-cut line of demarcation between the Achilles tendon coming down to the heel and the fat pad anterior to it. When swelling is inflammatory — caused by pus, hyperemia and fluid — a transudate obliterates these ordinarily clear-cut fascial planes; that is, they share in the inflammatory process and edema blurs the clear-cut demarcation. In this patient the swelling must at least in part have resulted from neoplasm or "cold pus" (which occasionally accompanies chronic actinomycosis or tuberculosis). I have excluded tuberculosis on clinical grounds alone. I think chronic osteomyelitis is out of the question, without some signs of healing or inflammatory soft-tissue reaction. We have here the *sine qua non* of tumor — namely, destruction with a soft-tissue mass.

In my everyday work this is where I should stop. I should say that this represented a malignant tumor of the bone and, because its origin was central, that it was not extrinsic invasion. I think that the prime responsibility is to try to make that distinction and not to go farther to give false security to the clinician.

The next question is, Was this primary or metastatic tumor? I should immediately have requested a skeletal survey to see whether there was any evidence of other metastases or any source for the tumor. In this case there was none. Metastatic tumors are exceedingly rare in the foot. A supplemental clue is that the tumor started in the center of the bone; most metastatic tumors, even those in the os calcis, begin at the terminal circulation in the ends of bones. At this point I draw a line because that is as far as one can go with reasonable assurance. From here on we should like to leave it up to the pathologist. I think that it should be emphasized that the important point now is that the mass should have been biopsied and all aspects of the case reviewed in the light of the findings. As academic play only I shall step over the line and speculate, and make it clear that this is speculation. This lesion probably represented the most common primary tumor in bone that starts in the marrow — namely, Ewing's sarcoma. It could have been an isolated myeloma or reticulum-cell sarcoma, but the age group, the central origin and the fact that it was entirely osteolytic make Ewing's sarcoma the best bet.

Clinical Diagnosis

Tumor, type unknown.

Dr. Martin H. Wittenborg's Diagnosis

Ewing's sarcoma.

Anatomical Diagnosis

Ewing's sarcoma of os calcis.

Pathological Discussion

Dr. Benjamin Castleman: Dr. Reidy did a needle biopsy, and this proved to be a Ewing's sarcoma.

Dr. Joseph Hanelin: I should like to thank Dr. Wittenborg for the excellent discussion; he is to be congratulated for nailing the diagnosis so well. We did not have the old films when we first saw the patient but considering the duration of the process favored a chronic inflammatory lesion. We wondered about tuberculosis until the tuberculin test was reported negative.

The patient has had a very gratifying response to irradiation, and in a short time there was marked regression of the soft-tissue swelling.

Dr. Marian W. Ropes: I think this is a very interesting case. I saw the patient only after the biopsy so that I did not have a chance to try to make the diagnosis. In retrospect I can see why those who followed her at first made the suggestion that she had inflammation or one of the connective-tissue diseases. In fact I still find it very difficult to explain the first episodes of swelling and pain with the entire subsidence between episodes. I should think this was an

unusual manifestation for such a long period for an ordinary Ewing tumor, but such cases have apparently been reported. The opinion was about equally divided between tuberculosis and malignant tumor, but the negative tuberculin test lowered the chances of tuberculosis and a malignant process seemed much more likely.

DR. JOHN A. REIDY: I first saw this child a few months after her first injury. At that time she had minimal swelling and very slight tenderness in the subastragalar region and some limitation of inversion and eversion. I thought the symptoms probably were the result of the injury and would subside. When she had another episode six months or so later I began to question whether it was a low-grade arthritis, and we carried on more or less on that assumption. We could not detect the minimal changes on these x-ray films. As soon as the mass actually began to grow it was obvious that it was something other than rheumatoid arthritis. I could not believe that rheumatoid arthritis could produce such extensive swelling, although occasionally it may. When with immobilization there was no improvement but a suggestion of increase in size we introduced a needle into the area that I had thought would probably survive; the skin was so tense that we thought it would break down if an operative approach was made through it. We aspirated only hemorrhagic exudate. Then we put the needle through the os calcis, which was very soft, and obtained enough tissue for a diagnosis.

DR. CASTLEMAN: The treatment for Ewing's sarcoma in this hospital is irradiation without amputation. I think the results that Dr. Milford D. Schulz has obtained with x-ray therapy have proved to be by far the more effective of the two types of treatment here. Is that what is done at the Children's Hospital?

DR. WITTENBORG: We do both. I think the most important single factor in the cure of any one patient is the presence or absence of metastases and location of the primary lesion.

DR. CASTLEMAN: As far as we know there is no evidence of metastases.

DR. HANELIN: That is correct.

DR. J. D. LEIDHOLT: I wonder whether Dr. Wittenborg remembers the patient at the Children's Hospital with a Ewing tumor of the talus that had a protracted course similar to this for over a year or two, and was first thought to be an aseptic necrosis. Cohen et al.[1] reported that case.

DR. WITTENBORG: How could I forget it? That was a Ewing tumor of the talus in a child about the same age that had been missed by both the clinicians and the radiologists. The presenting symptoms were those of collapse of the bone. There was a pathologic fracture that looked exactly like aseptic necrosis; I suspect that the mechanism was the same. The patient was believed to have aseptic necrosis and treated for that until the first metastasis appeared. That mistake can be made in any osteolytic metastasis in which there is a pathologic compression fracture and resulting increased density by compression, for one may then not suspect an underlying destructive lesion.

DR. PAUL D. WHITE: What is the prognosis in this case?

DR. WITTENBORG: The most important single factor in the prognosis is the presence or absence of metastases. In vivo methods of picking up metastases, particularly in Ewing's sarcoma, are very crude; the metastases have to be several millimeters in size before they are recognized. Isolated cures have been reported after both surgery and radiation. A great number of failures are attributed to the presence of metastases at the time of operation, which often show up six or eight weeks afterward. If the patient under discussion had no metastases I think she has a fair chance of cure by either radiation or surgery. I have no strong preference for one or the other except as determined by the location of the tumor.

DR. WHITE: Can you estimate the chances for cure?

DR. CASTLEMAN: I should think that one might apply the same principle to this tumor that is applied to other tumors that have been present for over two years. If by that time there are still no metastases, the prognosis is a great deal better. Of 22 patients with Ewing's tumor treated here with adequate irradiation 4, or 18 per cent, are alive after five years and are apparently cured.[2]

REFERENCES

1. Cohen, J., Brown, K. A., and Grice, D. S. Ewing's tumor of talus (astragalus) simulating aseptic necrosis. *J. Bone & Joint Surg.* **35A**: 1008-1012, 1953.
2. Wang, C. C., and Schulz, M. D. Ewing's sarcoma: study of fifty cases treated at Massachusetts General Hospital 1930-1952 inclusive. *New Eng. J. Med.* **248**:571-576, 1953.

CASE 41102

PRESENTATION OF CASE

A fifty-year-old man entered the hospital complaining of stomach trouble.

The patient had been well except for a "nervous stomach all his life" until nine weeks previously, when a sore throat, coryza and general malaise that lasted for three or four days developed. For three weeks he had experienced some anorexia and queasiness, with malaise. He was placed on belladonna therapy by his physician and was without pain and was better except for uneasiness for four days. The temperature was 99 to 100°F., and the white-cell count 12,000; his physician started him on a course of tetracycline hydrochloride (Achromycin) for three days. On the fourth day abdominal "bloating" developed, and he vomited. He had four or five attacks of abdominal distention, queasiness and subsequent vomiting three or four hours after a meal. He was slightly better on the day after an attack. Two weeks before admission he was admitted to another hospital, where gastrointestinal, gall-bladder and barium-enema examinations and a culture were reported as

negative. Five days before admission he had another attack of slight fever, abdominal distention and vomiting. Still another attack occurred on the day of admission, with a temperature of 101°F. There had been a 25-pound weight loss since the onset of the present illness. No history of tarry stools, diarrhea or constipation was elicited.

The past history revealed "yellow jaundice" for five or six weeks at the age of nine after a blow in the stomach. The only prior operation was a tonsillectomy and adenoidectomy at the age of ten.

Physical examination revealed a well developed, well nourished man in no distress. Significant findings included a split first mitral sound with a soft mitral systolic murmur at the apex. The liver edge was palpated 1 fingerbreadth below the right costal margin. The prostate was thought to be slightly enlarged, with no nodules.

FIGURE 1. *Posteroanterior View of the Barium-Filled Stomach and Duodenal Loop.*
The loop is wide, but this is probably within normal limits for a person of asthenic habitus. The distended loop of bowel in the left lower side of the abdomen is observed later in the five-hour examination to be distended small bowel.

The temperature was 99.6°F., the pulse 98, and the respirations 22. The blood pressure was 120 systolic, 70 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 14.6 gm. per 100 cc. and a white-cell count of 12,700, with 27 per cent neutrophils, 63 per cent lymphocytes, 7 per cent monocytes and 2 per cent eosinophils. The bilirubin was 0.5 mg., the total protein 5.5 gm., the albumin 3.1 gm., the globulin 2.4 gm., the nonprotein nitrogen 23 mg., the amylase 11 Russell units, and the alkaline phosphatase 2.9 units per 100 cc.; the sodium was 139 milliequiv., the chloride 99 milliequiv., the potassium 4.6 milliequiv., and the carbon dioxide 27 milliequiv. per liter. A bromsulfalein test showed 4 per cent retention of the dye in forty-five minutes. The erythrocyte sedimentation rate was 38 mm. in one hour, and the prothrombin time 45 per cent.

Initial stool specimens were reported as giving a ++ guaiac test. An x-ray film of the chest revealed

FIGURE 2. *Roentgenogram of the Gastrointestinal Examination Five Hours after a Barium Meal, Showing a Dilated Loop of Small Bowel (Arrows) in the Lower Left Side of the Abdomen and a Small Intestine of Normal Caliber in the Right Side of the Abdomen.*

no disease, and a gastrointestinal series was reported as showing widening of the duodenal loop and suggestion of partial small-bowel obstruction (Fig. 1 and 2).

In the hospital the patient continued to have episodes of crampy abdominal pain, nausea and vomiting. The temperature was elevated on the third and fourth hospital days to 99.6 and 100.6°F., but there was no consistent daily elevation. The vomitus was feculent, brown and bile colored. He also had several loose, jellylike, mucoid stools, which gave a ++++ guaiac test. Between attacks the abdomen was soft and nontender, with a normal peristalsis. On the fifth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM V. MCDERMOTT, JR.*: This is a very intriguing case and one in which Dr. Gibbons is going to have to help me. This debilitating illness was relatively acute unless the "nervous stomach,"

*Assistant in surgery, Massachusetts General Hospital.

about which we have no further information and which dated back some years, was related to the illness; the "nervous stomach" is hard to tie to the problem, as is the apparent upper respiratory infection nine weeks before entry. If I pass over those, I am left with this episode of three weeks' duration, which was characterized by intermittent low-grade fever, recurring attacks of abdominal distention, queasiness and subsequent vomiting that gave relief for a day. X-ray studies in another hospital were negative. There was a 25-pound weight loss in three weeks. The other findings on physical examination were not contributory. The hemoglobin was normal, possibly surprisingly so. There was an increase in the leukocytes, with an actual lymphocytosis. The sedimentation rate was elevated, and the prothrombin time depressed. The guaiac test on the stools was positive. The other laboratory findings were not remarkable and probably were not pertinent to the diagnosis. The x-ray findings, which are somewhat limited, may be of some help: they were described as a widening of the duodenal loop and a question of small-bowel obstruction.

Dr. John F. Gibbons: I see no evidence of an intrinsic lesion in the stomach or duodenum. The duodenal loop is widened, but this patient has a habitus in which the stomach is transverse so this widening may be due primarily to the habitus; at least, I am not able to say that an enlarged liver or head of the pancreas is compressing the duodenum (Fig. 1). The mucosa that I see in the duodenum appears normal. Initially, the colon contained a good deal of gas, and there is a distended loop of gas-filled small bowel in the left lower abdomen, which on a film made five hours after the barium meal is filled with barium (Fig. 2). There is a suggestion of obstruction in dilated small bowel at this point, but since we have no subsequent films, I am not sure at what level there may be obstruction; I am fairly sure that there is obstruction.

Dr. McDermott: Is that fairly low in the small bowel?

Dr. Gibbons: It is hard to say; at least we know that there is a great deal of barium-filled bowel that is of normal caliber; presumably the jejunum lies primarily to the right in this patient so that I should suspect that the obstruction is at least below the jejunal level. I see no abnormal soft-tissue masses and no unusual calcification.

Dr. McDermott: Can you tell anything about the mucosal pattern of the small bowel; is it normal?

Dr. Gibbons: No; it is not normal. The mucosa in this segment of small bowel appears definitely abnormal, although the granular pattern of the barium, which is mixed with fluid — and this is also suggestive of obstruction — does not enable one to outline the mucosa as well as it is outlined more proximally.

Dr. McDermott: There is no diffuse disease of small bowel that you see in the x-ray films?

Dr. Gibbons: No.

Dr. McDermott: I think the x-ray picture as described by Dr. Gibbons at least ties in with the clinical history. There is nothing specific on which we can base a diagnosis, but when all the facts are added together certain things become apparent. First of all the clinical history is compatible with a subacute small-bowel obstruction of about three weeks' duration, and the x-ray findings described bear that out. The level of the lower intestinal obstruction is not obvious without a barium-enema examination. It must have been in the small bowel, probably in the distal small bowel, for the x-ray findings and symptoms were not suggestive of high obstruction but more of incomplete distal obstruction. This type of picture could represent obstruction in the colon, particularly in the ascending colon or cecum, but there was no evidence to bear that out.

One thing that comes to mind immediately is the syndrome that has been described in the roentgenologic journals of carcinoma in the ascending colon, with subacute obstruction and metastases to the region of the superior mesenteric vessels, which cause a widening of the duodenal loop. The x-ray description makes that an attractive hypothesis, but I am inclined to discount that. I should agree with Dr. Gibbons that, although the duodenal loop is widened, in a man of this build the widening need not be significant.

The findings I do have to consider are the intermittent fever, the mild leukocytosis, with an actual lymphocytosis and with an increased sedimentation rate and the positive stool guaiac tests.

Dr. Benjamin Castleman: Dr. McDermott, there was another white-cell count of 11,200, with 58 per cent neutrophils and 39 per cent lymphocytes.

Dr. McDermott: From the information in the protocol I was going to stress the actual lymphocytosis, which apparently I cannot do now. One condition that will cause obstruction of the distal small bowel is an inflammatory granulomatous process such as regional enteritis. The diagnosis, as I see it, lies between regional enteritis and neoplasm. Can I distinguish between the two? Regional enteritis that causes recurrent bouts of fever and an elevated sedimentation rate usually implies an acute inflammatory process, whereas certain types of lymphoma can, by the disease alone, cause an intermittent fever and leukocytosis, which in the lymphosarcoma group particularly is characterized more by lymphocytosis than neutrophilic leukocytosis. In most of the cases of regional enteritis with fever and an inflammatory mass there is usually an actual increase in the neutrophils even though regional enteritis is a granulomatous process somewhat akin pathologically to tuberculosis. However, the lymphocytosis provides no specific differential. Stool guaiac tests may be positive in both lymphoma and regional enteritis. The number of patients with regional enteritis who have occult blood in the stools is relatively small compared to that of those

with lymphomas, which ranges up to 75 or 85 per cent.

The other neoplasms in the gastrointestinal tract I can mention and discard. I think there is very little evidence on which to make the diagnosis of carcinoma of the small bowel. Certainly, among the neoplasms of the small bowel, which are rare, carcinoma is about as common as lymphoma, but the pattern of the fever and the leukocytosis are more compatible with either lymphoma or regional enteritis. Moreover, it is not the pattern of a benign small-bowel tumor. Usually, these lesions — the neurofibromas and leiomyomas are the common ones in the small bowel — are manifested by anemia from occult bleeding over a long period or by acute episodes of small-bowel obstruction from intussusception.

To come to the point as quickly as possible, I shall narrow the diagnoses down to regional ileitis, relatively acute, causing distal-small-bowel partial obstruction, and lymphoma, probably a lymphosarcoma in the distal small bowel, giving the same pattern. Statistically, I think that regional ileitis is the more common, but the age is somewhat against this disease. It has been reported in the older age group, but fifty is about the upper range for the onset of the disease. If one wants to consider this "nervous stomach" as evidence of long-standing chronic gastrointestinal disease I suppose one could say that this was a stage of regional enteritis that had begun many years previously, but there was no further information about the "nervous stomach." I suppose if it had been characterized by bouts of diarrhea, I could tie it in more closely; as it is, I must discard that as noncontributory. Therefore, with the evidence of intermittent fever, partial distal-small-bowel obstruction of relatively acute duration, severe debility and 25-pound weight loss, mild leukocytosis with at least a relative increase in the lymphocytes (although the two smears were interpreted somewhat differently), the elevated sedimentation rate and the occult blood in the stool, I shall center on lymphoma of the distal small bowel.

One thing I have not mentioned is the prothrombin time, which was depressed. I do not think in the absence of any other sign or symptom suggestive of liver disease that this is significant. It may well be that either the problems of absorption in the intestinal tract, which were manifested by the 25-pound weight loss over a short period, or the fact that antibiotics had been given before admission or both accounted for a temporary depression of the prothrombin time.

Dr. Gibbons: I neglected to mention the spleen. I have been asked whether it is enlarged. It could be slightly enlarged, but I do not think so.

Dr. McDermott: I do not think that would help me one way or the other, particularly since you cannot be sure about enlargement.

Dr. Richard H. Sweet: I wonder if Dr. McDermott would include the possibility that the widened duodenal loops were due to lymphoma in the retropancreatic lymph nodes.

Dr. McDermott: I thought of that; I mentioned it earlier when I discussed the specific syndrome of the widened duodenal loop due to metastases from the ascending colon. If this means anything, it could obviously mean lymph-node metastases. I had discarded carcinoma of the pancreas.

Dr. Sweet: I was thinking not of carcinoma but of lymphoma with involvement of lymph nodes.

Dr. Castleman: This patient was seen by Dr. Baker. Perhaps he could tell us about his findings.

Dr. Myles P. Baker: Our preoperative diagnosis was lymphoma like Dr. McDermott's. I confess I did not consider regional enteritis. The previous history of "nervous indigestion" was, as Dr. McDermott suggested, irrelevant. This patient was as well as the next man. There was no suggestion that he had previously had enteritis. This illness involved repeated attacks of subumbilical discomfort with increasing nausea and vomiting and with them fever, followed by improvement for a few days so that one would think he was recovering, and then another bout. These attacks, with the weight loss, impressed us as manifestations of a progressive disease. After a two-month illness, we thought the low serum albumin was indicative of some underlying progressive disease such as lymphoma. One stool had old brown blood in it; the others gave positive guaiac tests. There was no mistaking that.

Dr. Castleman: One of the surgeons who saw the patient thought that the picture was that of jejunal obstruction because of the widening of the loop.

Dr. Baker: The patient was obviously getting worse and when within a couple of days of admission to the hospital he began to have fecal vomiting, we stopped studying him.

Clinical Diagnosis

Lymphoma of small bowel.

Dr. William V. McDermott, Jr.'s, Diagnosis

Lymphoma of distal small bowel.

Anatomical Diagnosis

Acute and chronic enteritis of jejunum.

Pathological Discussion

Dr. Castleman: This patient was operated on by Dr. Arthur W. Allen. Dr. Behringer, you assisted him; perhaps you can tell us what was found.

Dr. Glenn E. Behringer: Dr. Allen's preoperative diagnosis also was lymphoma. We believed that the solitary tumor in the small bowel, with evidence of considerable dilatation above it, could be accounted for on that basis. As Dr. Sweet said, the dilatation of the duodenal loop could also be explained by retropancreatic lymph nodes. At operation a tumor was found in the distal jejunum about 120 cm. from the ligament of Treitz. The perijejunal lymph nodes

were enlarged to about 2 cm. in size, and there was a fist-sized mass of lymph nodes at the base of mesentery. The duodenal loop did not appear altered in contour, and the spleen was normal in size. The jejunal mass had every appearance of an intramural lymphoma and was resected together with the perijejunal lymph nodes, and an end-to-end anastomosis was done.

DR. CASTLEMAN: I opened the specimen in the operating room and found a narrowed area about 6 cm. long in the jejunum in which there were hard, raised, corrugated rugae (Fig. 3). In the upper end, which was much more dilated, in some of these folds I felt small nodules in the submucosa of individual rugae, with ulcerations between them. I leaned toward a diagnosis of lymphoma grossly, but microscopical section of these raised rugae revealed that the mucosa was completely wiped out by an acute membranous process that extended down into the mucosa and obliterated all the mucosal glands. This proved to be an acute inflammation, with deposits of fibrin. The submucosa contained distended lymphatics; the process did not extend much below the submucosa. We made many blocks and found nothing specific—no granulomas to suggest a characteristic regional enteritis. The condition reminded me of the enteritis that follows the administration of antibiotics, but there was no history of the patient's having taken any.

DR. MCDERMOTT: He had tetracycline hydrochloride for three days.

DR. CASTLEMAN: But he had this disease before he was given the antibiotic, of which he received very little.

This was, then, an acute or perhaps subacute enteritis without granulomas, producing mild small-bowel obstruction. I suppose that the disease is some variation of regional enteritis. We have seen regional enteritis in the jejunum before; Dr. Chester M. Jones remembers a case of regional enteritis of the duodenum that he discussed at a clinicopathological conference.* The lymph nodes in the case under discussion were huge; some of them that Dr. Allen left in were about as large as an egg. He removed a number of them, which showed only chronic inflammation and hyperplasia. There was no evidence of neoplasm or lymphoma anywhere.

DR. BERNARD M. JACOBSON: Was the infiltration lymphocytic or polymorphonuclear?

DR. CASTLEMAN: Mostly a plasma-cell infiltration. At operation a rush frozen section revealed almost a pure culture of plasma cells so that I wondered whether this was a rare form of myeloma of the bowel, but on the fixed section they were merely inflammatory plasma cells.

DR. MCDERMOTT: It is unusual for regional enteritis to begin at the age of fifty.

DR. CASTLEMAN: It does not fit with the usual form of regional enteritis, but we do see inflammatory conditions of this type in the small and large bowel at all ages.

DR. SWEET: A year ago I operated on a fifty-eight-year-old colleague of ours who had never had a single grumble in his intestines before he was admitted to the hospital with acute small-bowel obstruction. He also had regional enteritis.

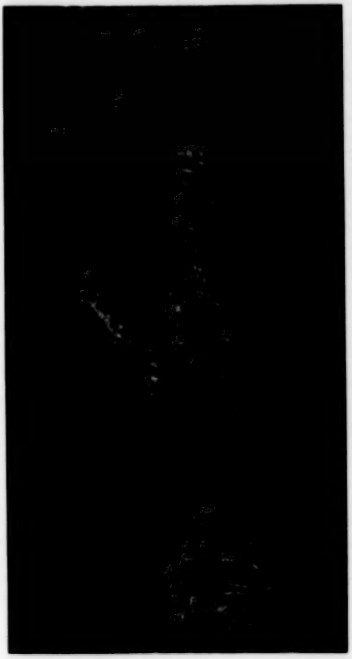

FIGURE 3.

DR. CHESTER M. JONES: The histology is not characteristic of regional enteritis.

DR. CASTLEMAN: There were no granulomas, but only half the patients have granulomas.

DR. GIBBONS: Apparently, the barium-filled bowel in the right upper quadrant was distal to the diseased bowel. Actually, we should have recognized that this was jejunum because when the ileum becomes this dilated, the valvulae conniventes are not usually so well shown.

DR. SWEET: Would not the relative position of that be in favor of its being jejunum too?

DR. GIBBONS: Yes; it would; but I assumed that the jejunum was on the right side, which happens occasionally.

*Case Records of the Massachusetts General Hospital (Case 35171). *New Eng. J. Med.* 240:692-694, 1949.

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"FRUIT AN HUNDREDFOLD"

AMONG the amazing advances that technical science has brought to the dissemination of medical information has been the closed-circuit television symposium or "videclinic." This new device, a natural step in the sequence of developments in communication that has included the medical chautauqua, the radio broadcast and the film library, has hitherto been used only on a limited scale; it has now really taken its place in the mass production of information useful to the professional audience.

Already, in February of this year, two of the world's greatest medical extravaganzas have been staged. The first of these, the country's initial nationwide clinical conference, consisted of the now historic noncommercial videclinic on the management of coronary-artery disease, produced and sponsored by Smith, Kline and French under the aegis of the American Medical Association and local and state medical societies. Covering 31 cities from coast to coast and from the Canadian border to New Orleans it was introduced by the president of the United States and was seen and heard by an estimated 22,000 physicians.

The second mammoth midwinter production, on the management of streptococcal infection and its complications, was sponsored jointly by the American Academy of General Practice and Wyeth Laboratories. Bigger, even, if no better than the preceding production, this impressive performance was presented simultaneously in 58 cities of the United States and Canada, from Quebec to California's City of the Angels; from Spokane to Miami. The panel of each of these gigantic presentations was composed of speakers and discussers from among the best the country can produce.

Spectacular, and wholly admirable as these ethereal pageants are, the part that they may play in that elusive and changing, yet basically stable process called education, is yet to be determined. They are certainly educational, to the degree that every human experience is educational, contributing in some way to the increased knowledge of the educable individual. Dollar for dollar, however, the question may be raised whether they are as educationally productive as a number of other less spectacular and more economical experiences may be — supervised service in an outpatient clinic, for example, the purchase of a textbook or even a subscription to a medical journal, if the time to read them is seized with determination. Of the many methods of instruction that have become available some are more effective than others, and some are more dramatic.

In view of a general concern over the rising and unmet costs of medical education in the very citadels of such learning, the process must surely be considered in terms of the national economy. Here at the basic undergraduate level of training every dollar that is vitally needed should be secured before any funds are diverted to more extravagant and less cer-

tain methods of instruction regardless of the publicity involved, however wholesome.

Industry, particularly the manufacture of pharmaceutical products, is today in a position of the utmost responsibility in relation to the real progress of medicine and the support of medical education. In assuming that responsibility it must put first things first. It must balance the safety and the usefulness of its goods against the terms in which they are extolled and the appeal that is built up around them. It must constantly have in mind that its own continuing financial success, in accord with the professional ethics that it regards so highly, depends on an unfailing supply of well trained graduates coming from the adequately staffed and equipped medical schools of the country; for if this educational structure were not maintained then the most respected commercial house would fall into a vacuum in which it would simply be peddling proprietary remedies. Industry must accept seriously the efforts that are being made toward its own education in the investment of its profits where they will be of the greatest benefit to mankind.

At the moment this investment should be primarily at the very foundation of medical education — in the medical schools and medical libraries of the nation — and only secondarily in the instruction and entertainment of the already confirmed practitioners.

ACTH, CORTISONE AND ASPIRIN IN ACUTE RHEUMATIC FEVER

THOSE who have known about the Cooperative Clinical Trial of ACTH, cortisone and aspirin in the treatment of acute rheumatic fever have been anxiously awaiting the reports of the results of that study. The first of these reports, dealing with the effects in children and including the first full year's follow-up observations, has just been published simultaneously in the March issue of *Circulation* and in the *British Medical Journal*. Four groups participated in the study: members of the Rheumatic Fever Working Party and United Kingdom participating centers; members of the Principal Investigators Subcommittee and United States participating centers; associated investigators at co-operating centers in both countries; and a group of statistical consultants. The participants included a large number of outstanding pediatricians, internists, clinical investigators, epidemiologists and statisticians in Great Britain, the United States and Canada who have long been interested in rheumatic fever and related subjects.

The joint planning of this co-operative effort and the working out of the design of the study required about six months for completion. It necessitated the establishment of definite criteria for diagnosis and for inclusion of patients, as well as a rigid and fool-proof system for the random selection of patients for each of the treatment groups. The patients were studied in a uniform manner and given a six-week period of treatment with predetermined dosage regimens, and a fixed pattern of clinical and laboratory observations, follow-up study and reporting.

The trial was designed to compare the therapeutic effects of ACTH, cortisone and aspirin on the course of acute rheumatic fever, all patients being treated in the hospital and on bed rest, and protected against infections with beta-hemolytic streptococci. Within the limitations imposed by the design of the study, answers were sought to two questions: the relative effectiveness of each of these hormones and aspirin in altering the course of the acute disease or in suppressing its clinical manifestations; and the relative effectiveness of these three agents in preventing rheumatic heart disease. Meanwhile, information was collected on the side effects of these three agents.

This report presents an analysis of the data obtained in about 500 children under sixteen years of age who were admitted to the study over a seventeen-month period ending on June 15, 1952. It compares the effects of the three drugs on the acute course of rheumatic fever through thirteen weeks from the start of treatment and on the persistence and development of rheumatic heart disease through the first year of follow-up observations.

The data collected in 6 collaborating centers in the United Kingdom, 5 in the United States and 1 in Toronto, Canada, are presented in considerable detail in a series of tables and charts covering all the clinical and laboratory observations that were available for analysis. In half the patients treatment was begun within fourteen days of the onset of the attack, and in nearly two thirds there was no history of a previous attack or evidence of pre-existing rheumatic heart disease. The treatments were therefore tested on patients of whom a large proportion were still in the early stage of the disease and had no established heart disease.

The three groups on ACTH (162 cases), cortisone (167 cases) and aspirin (168 cases) were remarkably similar in most respects at the start of the trial. The results of the treatment were measured in terms of separate manifestations of the disease — namely fever, pulse rate during sleep, erythrocyte sedimentation rate, joint involvement, chorea, erythema marginatum and nodules. The patients in the three groups were also compared for such aspects of the status of the heart as the heart size, atrioventricular conduction time and murmurs and, in particular, those indicative of serious illness — congestive heart failure and pericarditis.

The results were for the most part very clean cut. There was no evidence that any of the three agents resulted in uniform termination of the disease. On all three treatments fresh manifestations developed during treatment in some cases. Therapy with either of the hormones produced prompter control of certain acute manifestations, but this more

rapid disappearance was balanced by a greater tendency for the acute manifestations to reappear for a limited period on cessation of treatment. The use of the hormones also led to more rapid disappearance of nodules and soft systolic murmurs. At the end of a year, however, there was no significant difference between the three treatment groups in the status of the heart. During the period of treatment, observation and year of follow-up examination there were only 6 deaths among all the patients admitted to the study.

Obviously, many other methods of treatment could have been employed, but they would have increased the difficulties in the evaluation. The duration of treatment and even the dosage might have been altered, but there was no way of determining the optimum dose, or duration for all patients, or even for the individual patient. To introduce these variables would have decreased the significance of the data or required a greater number of patients than could be properly studied. That the dosage of the hormones could be considered reasonable is shown by the fact that the great majority of the patients who received them had some of the untoward side effects that result from their physiologic action. It seems unlikely that any major difference in the nature of the results could have been expected from juggling of the dosage regimens or from more detailed study.

No doubt some persons will retain their enthusiasm for the use of the adrenocortical hormones, nourished by the generally favorable external appearance of patients under their influence. Some of them may still harbor some deep-seated conviction that, somehow or other, this study did not tell the whole story and that, although equally valid data to contradict these findings may not be available, another design of study or a different method of presenting the results might have placed the hormones in a more favorable light. To be sure, the long-range effect of the hormones on heart disease remains to be determined. Certainly, after the full year of follow-up study, the results do not justify recommending treatment with ACTH or cortisone as a means of preventing rheumatic heart disease. These results place a heavy burden of proof on those who still hold a contrary view.

Those who proposed, planned, supported and offered advice and guidance in the conduct of this study deserve a great deal of credit. Those who actually participated in the collection, analysis and interpretation of the data are certainly to be congratulated for executing a difficult task in a most dispassionate and objective manner. This study, alongside the now classic co-operative studies on the chemotherapy of tuberculosis being conducted by the Veterans Administration in this country and the Medical Research Council in Great Britain and similar investigations by the Council and also by the United States Public Health Service, indicates that large-scale investigations of important therapeutic problems should be undertaken to solve major problems. The present study is all the more impressive because it involved so many significant persons in two countries and should serve as a model for international co-operation.

BRITISH COLLEGE OF GENERAL PRACTITIONERS

THE second annual general meeting of the British College of General Practitioners having been held on November 20, 1954, a brief comment on the progress that the College has made in its two years of existence will be of interest. The information is contained in the second annual report, published in the December issue of the *Practitioner*.

At the time the report was prepared the meeting had not yet taken place; the first general gathering had been held in the Great Hall of B.M.A. House on November 14, 1953, at which time Dr. William Norman Pickles, of Aysgarth, Yorkshire, was installed as the first president of the College. The Scottish Council was formed in the following month.

The total membership recorded as of the end of September, 1954, was 2967, consisting of 2539 members and 428 associates, of whom 345 were in the overseas contingents — 126 in Australia, 49 in New Zealand, 16 in Malaya, 71 in Eire and 83 in other countries. Canada's independent College of General Practice was established in June, 1954, and cordial relations exist between the two.

During the year the last regional faculties in the British Isles were formed, making 27 in all, including 5 overseas. These faculties are in a way analogous to the state academies of general practice in this country, operating as component parts of the whole. So far as possible each faculty is centered in a city with a university and a medical school.

Various activities have been planned, to be initiated by the College or for its participation. Among them two aspects of undergraduate education are under consideration — instruction in the problems of general practice by general practitioners, working with the medical schools through lectures and preceptorships, and the adaptation of medical-school curriculums to the teaching of general practice, with aid in the selection of students. Another important activity will be the continued development of postgraduate education through the planning and arranging of courses.

The promotion of research in general practice, in which the College's first president has set such a conspicuous example, will be one of the organization's major concerns. This will be carried on in various ways: through College-sponsored investigations, such as a study of the value of sulfonamides and antibiotics in preventing bacterial complications of measles, with 130 members participating, and

through faculty-sponsored and individual investigations.

The careful staff work that has gone into the organization of the College and the planning of its activities shows a zeal and an industry that will ensure its continuing value to the profession.

RED CROSS MONTH

THE days and weeks of special interest set aside for particular observance during February* may be supplemented by a reference to March, the month of the Red Cross campaign. In its annual appeal for members and funds, this great organization reminds all citizens of its service in time of need and of the fact that, in the words of President Eisenhower, "So long as human misery exists, Red Cross work can never be finished."

Recent disasters emphasize one aspect of this volunteer army's effort. Those who received emergency care in the Worcester tornado and the two hurricanes that battered the New England area can testify to the extreme necessity of this type of aid. But Red Cross help includes a host of other activities, far too numerous for even the briefest mention here; a few of them are the blood program, the provision of nurses's aides, home service and overseas help and advice for American troops with family and other problems, first aid in accidents, programs for water safety and home nursing.

Americans should need no urging to join and support the Red Cross since all of them, at one time or another, have been helped or have seen others helped through its efforts. A generous contribution in Red Cross month guarantees that a great national tradition — voluntary aid to all who need it — will be continued.

*Editorial. Ring out, wild bells. *New Eng. J. Med.* 252:244, 1955.

Bibliographical Notice. Error of Position, being a discussion of the ultra medical Position of the American Medical Association. . . . *This is an abusive and scurrilous attack on the Medical Profession of America, illustrated by an indecent engraving. The few who can wade through its pages will be disgusted with it.*

Boston M. & S. J., *March 15, 1855*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

WEST — Frederick O. West, M.D., of Woburn, died on December 30. He was in his seventy-second year.

Dr. West received his degree from Harvard Medical School in 1909. He was formerly chairman of the staff of the Choate Hospital, president of the Middlesex East District Medical Society and a member of the Woburn board of health. He was a fellow of the American Medical Association.

He is survived by his widow, three daughters and a son.

AMERICAN MEDICAL ASSOCIATION CLINICAL SESSION

SUBMISSION OF PAPERS

ABSTRACTS

Abstracts of papers to be offered for presentation at the Clinical Session of the American Medical Association in Boston, November 29 and 30 and December 1 and 2, 1955, must be submitted in *duplicate* before July 15, 1955, with an absolute deadline of August 1, 1955. They should be sent to Dr. Theodore L. Badger, chairman of the Program Committee, care of the Massachusetts Medical Society, 22 Fenway, Boston 15.

Titles of papers alone will not be considered by the Program Committee, and abstracts of subjects for presentation must be presented as described. Abstracts must be limited to a 300-word summary including important data and conclusions. Charts and tables should be attached to help in the selection of papers.

The names, titles, with hospital affiliation and complete addresses of all authors should be included in each abstract. The author who is to present the paper must be the first author listed in the abstract.

All abstracts and papers will be reviewed by the Program Committee and, when necessary, by experts in special fields to select those containing the most suitable material. *Final selection will be on a competitive basis.*

Subjects for presentation at the meetings may include clinical and scientific aspects of all branches of medicine and surgery, as well as the results of investigative work bearing on these subjects. Those wishing to present subjects of a confidential nature from the armed forces or other sources must clear the material through official channels *before* submitting the abstracts to the chairman of the Program Committee.

It is urged that all who desire a place on the program of the Clinical Session submit their abstracts as early as possible to facilitate the work of the Program Committee in competitive selection of papers. The deadlines, however, must be met. Authors are cautioned to remember the deadline of July 15, 1955.

PAPERS

Subsequent to review of the abstracts by the Program Committee, papers will be selected on a strictly competitive basis. Authors will be notified by September 15, 1955, if their papers are accepted for presentation.

Papers presented at the Clinical Session must be original contributions that have not previously been

presented or published. All such papers should be considered as belonging exclusively to the American Medical Association and should not be submitted for publication elsewhere without the advance permission of the American Medical Association.

The time allotted for presentation of papers will be twenty minutes.

THEODORE L. BADGER, M.D.
Chairman
Program Committee

MASSACHUSETTS DEPARTMENT OF MENTAL HEALTH

MASSACHUSETTS SURVEY OF COMMUNITY PSYCHIATRIC RESOURCES

In 1951 the Harvard School of Public Health conducted a survey of community psychiatric resources in Massachusetts for the Massachusetts Department of Mental Health. The survey was under the direction of Warren T. Vaughan, Jr., M.D., who is now director of the Division of Mental Hygiene, responsible for the development of area mental-health centers throughout the State. Copies of the survey were recently distributed to all clinics, hospitals and physicians participating in the survey and to 300 health and social agencies in Massachusetts. A limited number of copies are available, free of charge, to professional organizations interested in the mental health field. Application should be made to Warren T. Vaughan, Jr., M.D., Department of Mental Health, 15 Ashburton Place, Boston.

MENTAL-HYGIENE NEWS BULLETIN

The Massachusetts Department of Mental Health has begun a monthly mental-hygiene news bulletin, which will be sent on request to all agencies and professional people in Massachusetts who are interested in mental health. The material in the bulletin will be addressed primarily to professional personnel in the Department of Mental Health, the State hospitals and schools. However, material of more general interest may from time to time appear in the bulletin and may be submitted to the editor by any professional group working in Massachusetts in the mental-health field. Professional people who wish to be placed on the mailing list may write to Warren T. Vaughan, Jr., M.D., Director, Division of Mental Hygiene, 15 Ashburton Place, Boston, Massachusetts.

BOSTON MEDICAL LIBRARY

VICAIRE'S GASTRONOMIC BIBLIOGRAPHY

Originally published in 1890 the *Bibliographie gastronomique* of Georges Vicaire has been out of print since 1900. It was issued in an edition of 500 copies and has been available only at collectors' prices. A new reprint was recently published in London by Derek Vershoyle Academic and Bibliographical Publications, Limited, with an introduction by André L. Simon, a collector of gastronomic books, who issued a catalogue of his collection.

PRESSE MÉDICALE

La Presse médicale, Paris, published three times a week since 1873, issued a special de luxe Christmas number for 1954. Printed on good paper and well illustrated, this issue presents, in addition to the medical articles, three historical studies: Shakespeare and his knowledge of medicine, the professional life of the physician during the sixteenth to the middle of the nineteenth century, and the anatomic drawings of Géricault, 1791-1824. The last article is an important contribution to the history of anatomic illustration.

BOOKS OF UNUSUAL INTEREST

Ackerknecht* has written primarily an analysis of the work of Rudolf Virchow, the founder of "cellular pathology," and not essentially a biography, although thirty-six pages are devoted to a story of his life. The author has strictly limited himself to the accomplishments and opinions of Virchow and his contemporaries in the fields of pathology, German liberalism and anthropology.

In 1848 a movement in Germany for the improvement of the professional status of the physician began, and Virchow took a leading part in this activity, and published with his friends *Die medizinische Reform*, which was brought out weekly from July 10, 1848 to June 29, 1849. He was a leading figure in the *Generalversammlung*, the reform society that in the beginning united three fourths of the Berlin profession. The author, who spent twenty-five years studying Virchow and his period, is well qualified to tell the story of one of the great medical men of the time. Likewise, he was born and grew up in the same region in Germany as Virchow and was trained in medicine, anthropology and history. The text is divided into three main parts: the doctor, the statesman and the anthropologist, prefixed by the life history. Various indexes conclude the text. The book is an exceptional biography.

*Ackerknecht, E. H. *Rudolf Virchow: Doctor, statesman, anthropologist*. 304 pp. Madison: University of Wisconsin Press, 1953.

DICTIONARY OF ORGANIC COMPOUNDS

A new edition of a standard reference work, *Dictionary of Organic Compounds* (edited by Sir Ian Heilbron and H. M. Bunburg and others), dealing with the constitution and the physical and chemical properties of the principal carbon compounds and their derivatives, was published in London by Eyre and Spottiswoode in 1953.

PHYSICIANS IN SCIENCE AND OTHER FIELDS

Three books important in the activities of physicians have been added to the history section of the library:

The Doctor in History, Literature, Folk-Lore. Edited by William Andrews. 8°, cloth, 287 pp. Hull: William Andrews and Company, the Hull Press, 1896.

Bailey, H., and Bishop, W. J. *Notable Names in Medicine and Surgery.* 12°, cloth, 202 pp. London: H. K. Lewis & Company, Limited, 1944.

Monro, T. K. *The Physician As Man of Letters, Science and Action.* 12°, cloth, 212 pp. Glasgow: Jackson, Wylie and Company, 1933.

CORRESPONDENCE

F. P.

To the Editor: I was much interested in the editorial, "Local Medical Doctor," in the October 28 issue of the *Journal.* I quite agree with the correspondent on page 757 of the same issue who intimates that the term and its medical abbreviation, L.M.D., is patronizing in its connotation and therefore derogatory, although in all certainty that could not have been the intention of whoever originated the term. Unfortunately, as stated, the term "local" for some reason also suggests "yokel," which is perhaps the reason. Certainly, the medical student who hears this term year after year in medical school and in his internship later cannot help being impressed, subconsciously or otherwise, with the fact that it indicates an inferior type of physician whose ranks he should not consider joining, despite the great need for general practitioners at present.

It seems to me that if a simple shorthand designation is required to indicate the referring physician, and this does appear to be so, it would be very practical to substitute for "local medical doctor" the term "family physician" and abbreviate this as F. P. I do not see how this term could be interpreted in any derogatory sense because many families not only regard a general practitioner as their family physician but also extend this term to mean their favorite internist, pediatrician or even surgeon.

I have tentatively introduced this term on my pediatric service at Genesee Hospital, where it has been well received by the house staff and the students and assistant residents who rotate through the service from the University of Rochester School of Medicine and Dentistry.

It would probably be best to refer this problem to the American Academy of General Practice, and, for this reason, a copy of this letter has been forwarded to Dr. William P. Hildebrand, president of the Academy.

Jerome Glaser, M.D.
Pediatrician-in-Chief
Genesee Hospital
Rochester, New York

CHRISTIAN SCIENTIST VIEWS *"PARENS PATRIAE"*

To the Editor: Rather belatedly the article, *"Parens Patriae,"* by C. C. Cawley, in the November 25 issue of the *Journal,* has come to our attention, and I should like to comment briefly on it so far as it refers to Christian Science.

Mr. Cawley starts, somewhat surprisingly, by relating in sober seriousness Mark Twain's "tall tale" about the supposed ministrations of a "Christian Science doctor" when he fell over a "75-foot cliff" and landed at the bottom "an incoherent mass of compound fractures." Besides an ignorance of Mark Twain's humor, the use of this story to introduce his subject seems to show that Mr. Cawley is ignorant of the humorist's final appraisal of Christian Science, recorded by his biographer, Albert Bigelow Paine, and confirmed by his daughter, Clara Clemens: "Christian Science is humanity's boon . . . Mrs. Eddy has organized and made available a healing principle that for two thousand years has never been employed, except as the merest kind of guesswork. She is the benefactor of the age."

Mr. Cawley then relates the story of a boy with a broken leg whose father, allegedly a Christian Scientist, refused to allow a doctor to set the leg, until compelled by force. Mrs. Eddy's own teaching on this subject is explicit. In *Science and Health with Key to the Scriptures* (p. 401) she writes: "Until the advancing age admits the efficacy and supremacy of Mind, it is better for Christian Scientists to leave surgery and the adjustment of broken bones and dislocations to the fingers of a surgeon, while the mental healer confines himself chiefly to mental reconstruction and to the prevention of inflammation. Christian Science is always the most skilful surgeon, but surgery is the branch of its healing which will be last acknowledged."

She goes on to speak of the reports of authenticated cases in her possession of the healing of broken bones through Christian Science alone; and healings of this sort — in many cases confirmed by subsequent x-ray studies that have shown a perfect setting and knitting of the bone — continue to appear among the verified testimonials in our periodicals. But the general rule quoted from *Science and Health* still stands, except where a person himself chooses to rely wholly on spiritual means in such a case.

The one court decision cited by Mr. Cawley that has to do with Christian Science is *Rex v. Lewis* (1903), which resulted in a verdict of manslaughter against a Christian Scientist. This goes back to the beginning of the century, when there was little general understanding of the nature and efficacy of spiritual healing. Both public and legal regard of Christian Science have changed since then. Increasingly, the states have tended to enact statutes by which it is provided that Christian Science treatment meets the requirements of medical attention. We would draw your attention particularly to the recent amendment in New York, where the statute requiring parents to supply their minor children with necessaries was expressly amended to protect Christian Scientists.

Mr. Cawley refers to an article by I. H. Rubenstein on "Faith Healing" published in the *Journal* in 1941. We would also refer to an answer to that article that appeared in your letter columns in April of that year, written by Herbert W. Beck, then manager of the Christian Science Committees on Publication.

In his reply Mr. Beck quoted Chief Judge Barber, of the Court of Appeals of New York, in a case cited by Mr. Rubenstein: "I deny the power of the legislature to make it a crime to treat disease by prayer." The subsequent actions of the New York and other state legislatures in implementing the Christian Scientist's right to provide for his children the form of treatment that he has found most efficacious in his own life bears witness to the growing recognition of this basic religious right. It also bears witness to the impression made on the community by the constantly growing mass of evidence that Christian Science is a genuine and effective healing agent.

Will B. Davis, *Manager*
Committees on Publication
First Church of Christ, Scientist
Boston, Massachusetts

OPTIMISM QUALIFIED

To the Editor: The patient with pulmonary histoplasmosis treated with cortisone and MRD-112 who was described by Michael and Vogel in the November 25 issue of the *Journal* was readmitted to this hospital just before the article's publication. Although his pulmonary lesions had not recurred, development of serious cerebral involvement makes it necessary to qualify the optimism expressed by the authors. When it is possible to evaluate the results of further therapy a follow-up report is contemplated.

J. H. Peters, M.D., *Chief*
Investigative Medicine Services
Veterans Administration Hospital
Atlanta, Georgia

HERNIATION OF FAT AND LOW-BACK PAIN

To the Editor: I read with interest the article in the December 30 issue of the *Journal*, entitled: "Herniation of Fat through Lumbodorsal Fascia as a Cause of Low-Back Pain," by Drs. Bonner and Kasdon. The authors rightly point out the importance of including this "fairly rare syndrome" among the possible causes of low-back pain.

They do not mention, however, that this syndrome was first described by Ackerman and me in the *Quarterly Journal of Medicine* for July, 1944, and later in the *Archives of Internal Medicine* for January, 1947. I have received a number of letters commenting on this omission and urging me to write to you. I am accordingly venturing to do so.

W. S. C. Copeman, M.D., F.R.C.P.
London, England

Note: The authors made no claim for originality, stating at the beginning of the report that the syndrome is not new. It is always a pleasure, however, to give credit where credit is due.—Ed.

REGARDING L. E. PHENOMENON

To the Editor: I am writing regarding the article in the January 27 issue of the *Journal* by A. M. Paull, M.D., entitled "Occurrence of the 'L.E.' Phenomenon in a Patient with a Severe Penicillin Reaction."

According to my interpretation of this article Dr. Paull is presenting the case as one of a false-positive L. E. test occurring in a patient with a severe penicillin reaction. However, certain discrepancies appear in the discussion. The first mention of a positive L. E. reaction in this patient appears in the listing of the findings *on admission*, when the patient had a diagnosis of pneumonitis and congestive heart failure and was treated with, among other things, penicillin. There is no mention of recent previous penicillin therapy. About fourteen days after the start of the penicillin therapy signs of a reaction developed, including urticaria, dysphagia and arthralgia. Another L. E. preparation at this time was found to be positive.

Thus, it seems to me that this patient had a positive L. E. reaction before he received any penicillin, unless his physician gave him penicillin — a possibility that was not mentioned in the report. If the positive test was found before any penicillin was given I do not see how Dr. Paull can attribute it to a penicillin reaction; some other explanation must be found.

I should appreciate it if you would clear up this rather important matter. I am not the only one who was confused by the report.

Marshall Smith, Jr.
Philadelphia, Pennsylvania

Mr. Smith's letter was referred to Dr. Paull, who offers the following reply:

To the Editor: Regarding the confusion that exists in Mr. Smith's mind, let me clarify the point in question. Initially, the patient was treated for congestive heart failure and chronic lung disease, receiving penicillin, digitalis and Thiomerin. Approximately two weeks after penicillin had been discontinued he was discharged, only to return thirty-six hours later complaining of pruritus, dysphagia, arthralgias and a skin rash. At this time we identified L. E. cells in the peripheral blood (using the technic described in the article).

I hope that this will alleviate the confusion.

A. M. Paull, M.D.
Providence, Rhode Island

GAMMA GLOBULIN AND HEPATITIS

To the Editor: It has been suggested that the success of gamma globulin in stopping an epidemic of infectious hepatitis in an institution for the mentally retarded, as reported in my article in the March 11, 1954, issue of the *Journal*, was more apparent than real, and that the decline in incidence of new cases was due to the fact that the epidemic had reached its natural peak. However, further developments at the institution make it quite apparent that immunity conferred by gamma-globulin inoculations really did bring the epidemic under control.

On August 28 another case of frank jaundice occurred in a hall where all the employees but only 20 inmates had been inoculated. This case was in a child who had been admitted to the institution in May. A second case developed on September 19, again in a child admitted in April of that year. Frank jaundice appeared in this child on September 30. Meanwhile, a wave of digestive upsets began to pass through the hall. Thirty other inmates became ill between September 27 and October 3, and 14 during the next week. Frank jaundice occurred in 2 more cases on October 2 and 12. The hall was placed on strict quarantine on October 2. Gamma globulin was given to all susceptible employees and inmates from October 8 to 12. The dosage employed was 0.005 cc. per pound of body weight, according to the recommendations made by Drake and Ming in the August 7 issue of the *Journal of the American Medical Association*. No more cases of frank jaundice occurred, but 40 more inmates manifested suspicious symptoms between October 10 and December 17. In all, 87 of a total population of 134 were ill in this three-month period. (Sixteen others were out on trial visit during this time.) None of the frankly jaundiced patients had received gamma globulin.

It is the opinion of the staff that this reduced dosage of globulin was less successful in controlling symptoms than the larger dose of 0.01 cc. per pound of body weight. Many of the children had recurrent bouts of nausea and vomiting. This was not true in the halls where the larger dosage was employed.

The only laboratory tests for hepatitis were those for determining bile and urobilinogen in the urine. The latter was discarded when it was found that a large number of persons in this hall and in other halls, including new healthy employees, had elevated urobilinogen values.

Salmonella infection was ruled out by cultures of the stools. Two inmates with symptoms have now been given diagnoses of pityriasis rosea, and a third one of infectious mononucleosis. The last patient had infectious hepatitis with jaundice on July 6.

Nine of the 14 previously jaundiced patients continued to have bouts of vomiting. One of these children was ill off and on all summer and by mid-October definite signs of portal cirrhosis had developed. It is possible that this child served as a continuous source of infection.

Whether or not the lower dosage was less effective than the higher cannot be said at this time. This period of study was in the fall and winter, when the attack rates of hepatitis and also intercurrent illnesses are high. The hall was in strict quarantine and ill children were kept there, rather than being transferred to the hospital. There was little in the way of recreational diversion and no schooling for the children; conceivably complaints could have been exaggerated by ennui. No patients with jaundice had previously been inoculated.

Alta Ashley, M.D., M.P.H.
District Health Officer
State of Maine Department of Health and Welfare
Augusta, Maine

BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Psychiatric Aide: His part in patient care. By Alice M. Robinson, R.N., M.S., director of nursing service and nursing education, Boston State Hospital. With a foreword by Walter E. Barton, M.D. 8°, cloth, 186 pp., with illustrations. Philadelphia: J. B. Lippincott Company, 1954. $3.00.

The author stresses the relations with the patient and the family. This is a practical manual discussing the various aspects of the work of a psychiatric aide. The appendixes provide a list of definitions, a reading list for further study and a brief classification of mental illness.

NOTICES

CORRECTION

In the *Journal* of December 16, 1954 (page 1022) Dr. J. T. Peters was listed as visiting professor of medicine, Louisiana State University School of Medicine. The appointment of Dr. Peters terminated on July 1, 1947.

AMERICAN COLLEGE OF CARDIOLOGY

The fourth annual convention of the American College of Cardiology will be held at the Hotel Biltmore, New York City, May 18-20.

There will be symposiums on hypertension and hypertensive heart disease, advances in cardiac surgery and the heart and circulation in sports. Dr. Ashton Graybiel will preside. Further information may be obtained from Dr. Philip Reichert, 140 West 57 Street, New York 19, New York.

MASSACHUSETTS HEART ASSOCIATION (KIDNEY SECTION)

A meeting of the Kidney Section of the Massachusetts Heart Association will be held in Morse Auditorium, Museum of Science, Boston, on March 28 at 8 p.m. The program is as follows:

Heart in Renal Disease. Dr. Harry A. Derow.

Current Status of Renal Transplantation. Dr. John P. Merrill.

Nephropathy of Potassium Depletion. Drs. William B. Schwartz and Arnold S. Relman.

Interested physicians and medical students are invited.

AMERICAN INSTITUTE OF DENTAL MEDICINE

The annual meeting of the American Institute of Dental Medicine will be held at the Desert Inn, Palm Springs, California, October 23 to 27. Among the speakers will be Drs. Maury Massler, Valy Menkin, Hans Selye, Reidar F. Sognnaes and Wendell L. Wylie. Further information may be obtained from Miss Marion G. Lewis, 2240 Channing Way, Berkeley 4, California.

POSITIONS AT NORFOLK NAVAL SHIPYARD

The Norfolk Naval Shipyard, Portsmouth, Virginia, announces vacancies for civilian doctors in the field of industrial medicine. Salaries range from $5940 to $8360 per year. The usual Civil Service qualifications are required.

NEW ENGLAND PEDIATRIC SOCIETY PRIZE

To stimulate interest in clinical investigation and accurate reporting of pediatric problems the New England Pediatric Society offers an award of $200 for the best paper submitted by an intern, resident or fellow who is connected with a hospital or medical school in New England and who graduated from medical school not more than five years ago.

The paper should concern one or more pediatric cases, of special interest or significance, with appropriate supporting literature and discussion. Papers should be submitted to Dr. Harry Shwachman, Secretary, New England Pediatric Society, 300 Longwood Avenue, Boston 15, Massachusetts, before July 31. The prize paper will be submitted for publication in the *New England Journal of Medicine*.

SOCIETY MEETINGS AND CONFERENCES

March–April. Postgraduate Medical Institute. Page 451, issue of September 9.

March–May. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.

March 14–30. Consultation Clinics for Crippled Children in Massachusetts. Page 328, issue of February 24.

March 15. South End Medical Club. Page 371, issue of March 3.

March 21–23. Aero Medical Association. Page 371, issue of March 3.

March 21–April 18. Hartford Medical Society. Page 289, issue of February 17.

March 22. Norfolk District Medical Society. Page 371, issue of March 3.

March 23–26. International Academy of Proctology. Page 876, issue of November 18.

March 25. Postgraduate Course in Occupational Medicine. Page 922, issue of November 25.

March 28. Massachusetts Heart Association (Kidney Section). Notice above.

April 1. American Psychiatric Association (Massachusetts District Branch). Page 289, issue of February 17.

April 1. New England Society of Anesthesiologists. Page 289, issue of February 17.

April 2–May 7. Middlesex South District Medical Society. Postgraduate Course. Page 758, issue of October 28.

April 5. Microcirculatory Conference. Page 289, issue of February 17.

April 6 and 7. American Heart Association. Page 371, issue of March 3.

April 7–9. Postgraduate Course in Obstetrics and Pediatrics. Page 329, issue of February 24.

April 8. Massachusets Society for Research in Psychiatry. Page 679, issue of October 14.

April 13. Chelsea Soldiers' Home. Page 329, issue of February 24.

April 13. New England Surgical Society. Spring Meeting. Massachusetts Memorial Hospitals and Boston University School of Medicine.

April 21 and 22. New York Academy of Medicine (Eastern States Health-Education Conference). Page 922, issue of November 25.

April 28–30. American Goiter Association. Page 329, issue of February 24.

April 30. State University College of Medicine at New York City. Page 289, issue of February 17.

May 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.

May 17–19. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

May 18–20. American College of Cardiology. Notice above.

June 5 and 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.

June 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

August 28–September 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.

October 23–27. American Institute of Dental Medicine. Notice above.

November 6–13. Second International Congress of Allergology. Page 157, issue of January 27.

November 29–December 2. Interim Session of the American Medical Association. Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, MARCH 17

THURSDAY, MARCH 17

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:45-9:45 a.m. Cardiac Grand Rounds. Yamins A, Beth Israel Hospital.

*9:00-10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00-10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00-11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.-12:00 m. Thoracic Conference. Modern Concepts in the Surgical Treatment of Pulmonary Tuberculosis. Dr. John B. Peter. Main Amphitheater, Peter Bent Brigham Hospital.

*11:00 a.m.-12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m.-12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.-1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*12:00 m.-1:00 p.m. Boston City Hospital Teaching Conference. Premature Separation of the Placenta and Afibrinogenemia. Dr. Duncan Reid. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

*12:15-1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.

*4:00-5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

FRIDAY, MARCH 18

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30-11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.-1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00-5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

*4:00-10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, MARCH 19

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00-9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

*8:30-10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00-10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.-12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

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